PSJ2 Exh 6

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Opioid Analgesics

A Treatment Primer

Opioid analgesics have been a mainstay of pain management for many decades. In recent years, there have been great advances in our knowledge of the pathophysiology and treatment of pain, as well as the pharmacodynamics of systemic opioid analgesics. This slide kit will discuss some of the key principles associated with pain management therapy and the clinical application of opioid analgesics.

The learning objectives for these slides are to:

Describe various classifications of pain - acute/chronic, nociceptive/neuropathic

Define and describe key opioid concepts of tolerance, physical dependence, addiction, pseudoaddiction

Discuss methods of pain assessment & measurement

List various indications for opioid medications

Describe commonly used opioids in terms of pharmacology, adverse events, & appropriate dose titration.

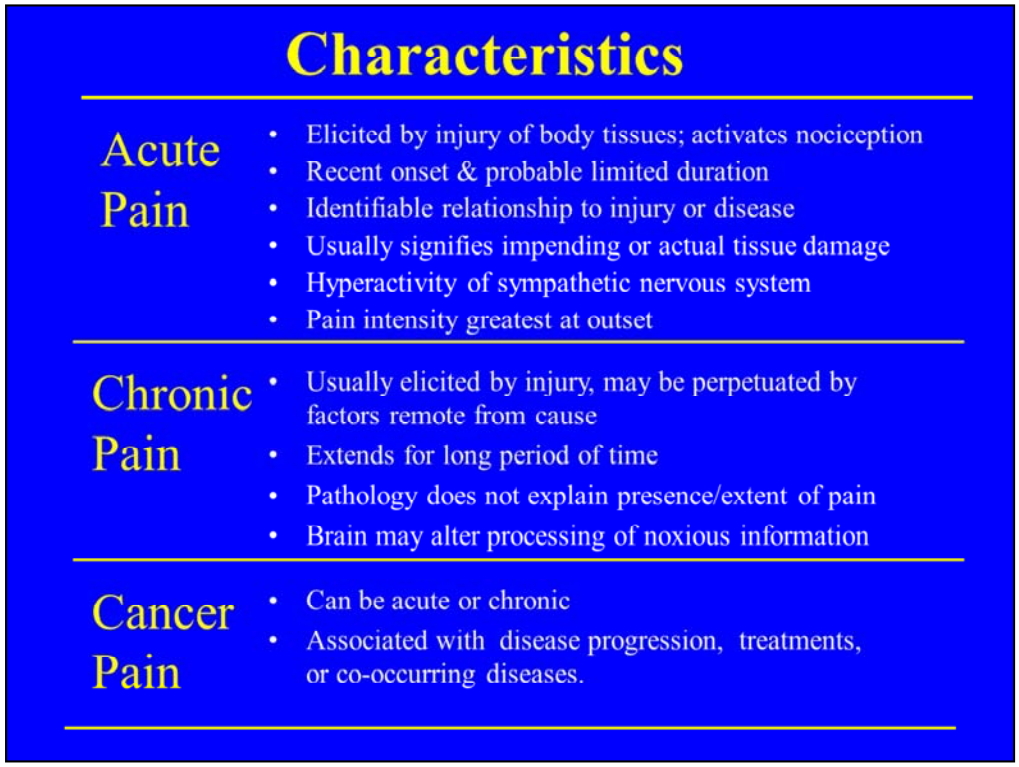
The most widely accepted definition of pain, adopted by the International Association for the Study of Pain (IASP) and the American Pain Society (APS) is shown in this slide.[1]

This definition describes pain as a phenomenon with multiple components that makes an impact on a person's psychosocial and physical functioning. It acknowledges the complexity of the pain experience. Pain is not determined by tissue damage alone. In fact, no predictable relationship exists between identifiable tissue injury and the sensation of pain. For example, a patient's description of pain may be disproportionate to the evidence of tissue damage. In times of high stress and trauma, pain may be described as less severe than one might expect; whereas patients with chronic nonmalignant pain (CNP) may describe pain for which little or no tissue damage can be found. The latter may be due to abnormalities in the neural processing of stimuli. The inability to identify tissue damage sufficient to explain the pain is not proof that the pain is of psychologic origin.[2]

Pain is always subjective. Objective observations of grimacing, limping, and tachycardia may be useful in assessing the patient, but these signs are often absent in patients with chronic pain known to be caused by structural lesions. There is no neurophysiological or chemical test that can measure pain. The

clinician must accept the patient's report of pain.[3]

1. Merskey H, Bogduk N (eds.). *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*, 2nd ed. Seattle: IASP Press, 1994:209-214.
2. Pasero C, Paice JA, McCaffery M. Basic mechanisms underlying the causes and effects of pain. In: McCaffery M, Pasero C (eds). *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:16-17.
3. American Pain Society (APS). *Principles of analgesic use in the treatment of acute pain and cancer pain*, 4th ed. Glenview, IL, 1999:3.



Acute pain is pain elicited by injury of body tissues, which activates nociceptors (nerve receptors which convey information about tissue trauma or damage to the central nervous system). [1] Acute pain infers pain of recent onset and probable limited duration. It usually signifies impending or actual tissue damage, and has an identifiable relationship to injury or disease. Acute pain precipitates an abnormally-enhanced response of the sympathetic nervous system, with accompanying increases in heart rate, blood pressure, and general sympathetic tone. Acute pain intensity is greatest at the onset, with gradual reduction of pain as healing takes place. If unrelieved, however, acute pain can persist with harmful physiological and and clinical effects. [1, 2]

Chronic pain is usually elicited by injury, but may be perpetuated by factors pathogenetically & physically remote from the original cause. Chronic pain extends for long period of time and its pathology does not explain presence and extent of pain. Additionally, the brain

may alter processing of noxious information to reduce or augment its effect. [1]

Pain associated with cancer can be acute or chronic and includes pain associated with disease progression, cancer treatments, or co-occurring diseases. [1]

1. Turk DC, Okifuji A. (2001) Pain Terms and Taxonomies of Pain. In Loeser JD ed, Bonica's Management of Pain, 3rd ed, p 17-19. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo: Lippincott Williams & Wilkens.
2. Cousins, M. (1994) Acute and postoperative pain. In Wall, P. & Melzack, R. eds, Textbook of Pain, pp 357-385. Edinburgh, London, Madrid, Melbourne, New York, Tokyo: Churchill Livingstone.

Clinical assessment of a patient with chronic pain should be undertaken with the specific goals listed on this slide. However, a crucial first step in diagnosing and treating pain is to acknowledge to patients that they are experiencing pain and that the pain is real.

Some patients with neuropathic pain will have an underlying disorder that can be cured or improved with disease-specific therapy, eg, B-12 deficiency neuropathy or an entrapment neuropathy. If you miss the diagnosis, you miss an opportunity to help your patient.[1]

All patients suspected of having neuropathic pain should be questioned about their pain history and receive a pain-specific sensory examination, a musculoskeletal and myofascial evaluation, and a basic psychological assessment.

A patient's functional status can be assessed by evaluating their ability to perform the activities of daily living (ADLs) as well as their mood, ability to sleep, and coping skills.

Psychosocial factors, such as anxiety, depression, posttramuatic stress disorder, substance abuse, or work issues, may complicate treatment responses, and may require specific intervention.

Obtaining a specific pain diagnosis is important because it enables physicians to formulate a more specific and targeted treatment plan.

The pain assessment should help the physician decide if multidisciplinary intervention is needed from a pain medicine specialist, a psychologist, psychiatrist, and vocational counselor.[2]

Shortcut to patient pain assessment:

P = palliating and precipitating factors

-Investigating palliating and precipitating factors can help the clinician establish the pathophysiologic frame of reference in which the patient experiences their pain.

Q = quality

-The quality of the pain may help diagnose the disease and the selection of appropriate treatments.

R = radiating or pattern

-The radiating or pattern nature of the pain gives insight into the extent, nature, and level of injury.

S = severity

-Severity of pain is a subjective, but important, measure. Similar injury may result in debilitating, tolerable, or unnoticed pain, depending on the individual patient.

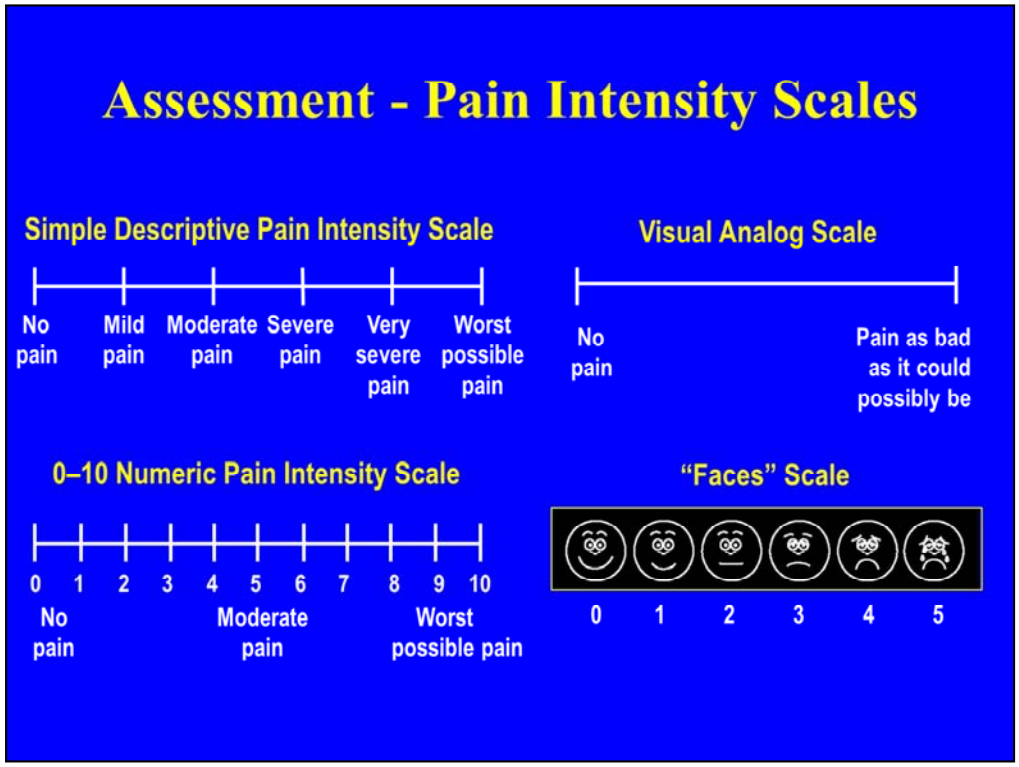
T = temporal nature

-Temporal factors may provide further insight into the extent, nature, and level of injury.

U = you (QOL)

-The most important goal in patient assessment is to gain insight into the patient. Restoring function and well-being, and providing understanding and hope may be the most important factors in improving the patient's quality of life.[3]

1. Katz N. Neuropathic pain in cancer and AIDS. *Clin J Pain*. 2000;16(suppl 2):S41-S48.
2. Backonja M-M, Galer BS. Pain assessment and evaluation of patients who have neuropathic pain. *Neurologic Clinics*. 1998;16:775-789.
3. Galer BS, Dworkin RH. *A clinical guide to neuropathic pain*. Minneapolis: McGraw-Hill Companies, Inc., 2000:8,20,37,38,45-48.



Four examples of commonly-used pain intensity scales are shown.

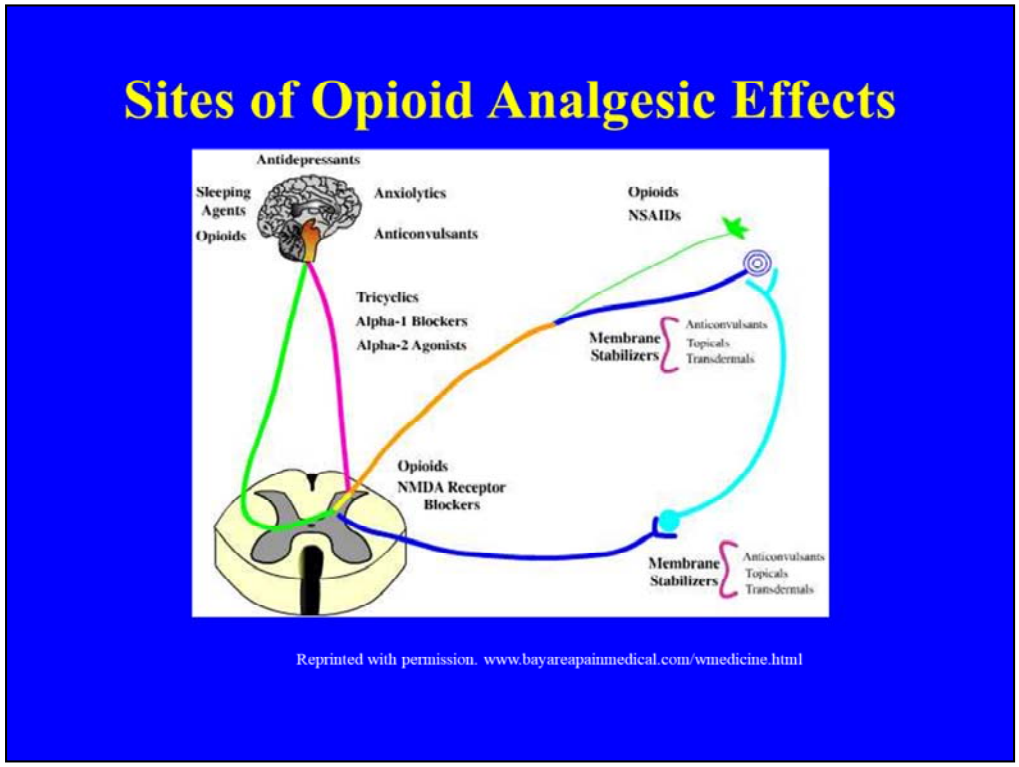
These scales are considered simple for patients to use as well as being a valid method for measuring the severity of pain. These scales can be used at the patient's bedside, and patients can be asked to respond to either a spoken or written question. With some scales, especially the visual analog scale, the patient marks the line at the point that best indicates the pain's intensity.[1,2,3]

Pain rating scales used in daily clinical practice generally deal with pain intensity, that is, how much a person hurts. Numerous scales for measuring pain intensity exist, and they have been referred to by many different names. Each scale has no standardized title or definition.[4]

1. Acute Pain Management Guideline Panel. *Acute pain management: operative or medical procedures and trauma. Clinical practice guideline.* AHCPR Pub. No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. Feb. 1992:116.
2. Whaley L, Wong DL. *Nursing care of infants and children*, 3rd ed. St. Louis: The C.V. Mosby Company, 1987:11.
3. Portenoy RK, Kanner RM. Definition and assessment of pain. In: Portenoy RK, Kanner RM (eds.) *Pain management: theory and practice*. Philadelphia: FA

Davis Company, 1996.

4. McCaffery M, Pasero C. Assessment. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:62.



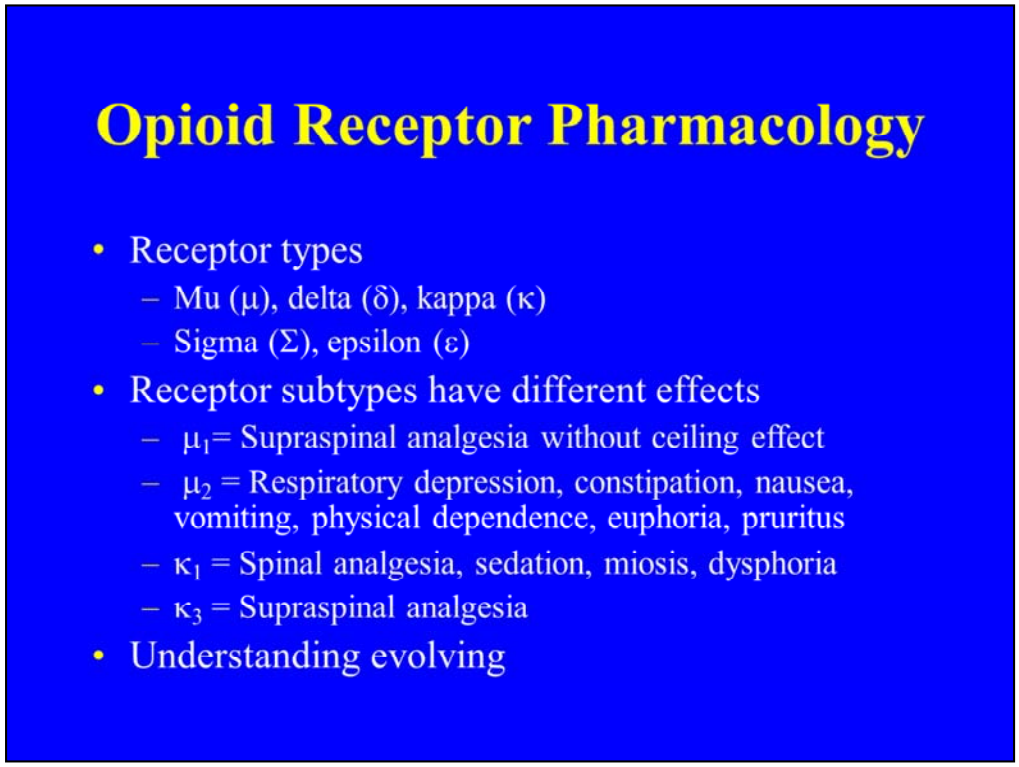
This diagram shows the sites where various medications exert their analgesic effects.[1]

Opioids produce analgesia produce analgesia by binding to specific receptors (mu, kappa, delta, sigma & epsilon) in the brain and spinal cord. Nociceptors carrying information about noxious stimuli from the periphery terminate in the dorsal horn of the spinal cord. In the dorsal horn, they they impair or inhibit the transmission of nociceptive input from the periphery to the CNS, by blocking the release of neurotransmitters such as adenosine triphosphate, glutamate, and substance P. [2,3,4] In the basal ganglia, opioids activate a descending inhibitory system that modulates peripheral nociceptive input at the spinal cord level. In the limbic system, opioids alter the emotional response to pain, making it much more bearable. [2]

Traditionally, opioids were thought to produce analgesia only through the CNS. However, opioid receptors have also been found in the periphery. Recent research shows that opioids have peripheral antiinflammatory actions, and also bind to receptors in peripheral nerve cells to block release of substance P.[3,4,5]

1. www.bayareapainmedical.com/wmedicine.html, Reprinted with permission.

2. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed., pp 1689-90, Philadelphia: Lippincott Williams & Wilkins, 2001.
3. McCaffery M, Pasero C. *Pain: Clinical manual*, 2nd ed., p22, 165-166, St. Louis: Mosby, 1999.
4. Portenoy RK. Basic mechanisms. In: Portenoy RK, Kanner RM (eds.) *Pain management: Theory and practice*. Pp 19-39, Philadelphia: FA Davis Company, 1996.
5. Stein C, Yassouridis A: Peripheral morphine analgesia, Pain 71: 119-121, 1997 (editorial)



Opioid receptors are located in the CNS, pituitary gland, and the GI tract. Opioid receptors have been found also on peripheral terminals of sensory nerves and cells of the immune system. Three major classes or types of opioid receptor sites are involved in analgesia: mu, delta, and kappa. When a drug binds to any of these receptor sites as an agonist, it produces analgesia. Opioid drugs that produce analgesia all have agonist effects at one or more of the opioid receptor site types.[1,2]

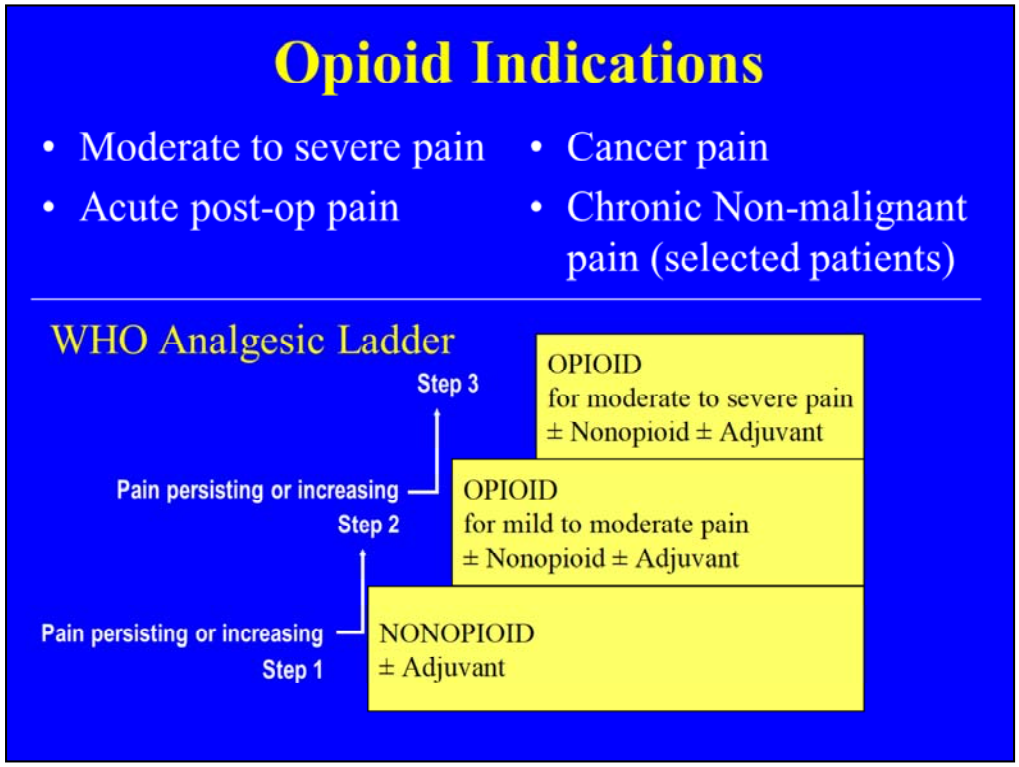
The type of opioid receptor site and its location determine the effects an opioid drug produces. In addition to producing analgesia, opioid drugs produce a number of other effects, including constipation, nausea and vomiting, sedation, respiratory depression, and urinary retention.[1,4]

Opioids have pharmacologic effects on almost every organ and function in the human body. Some of these effects are beneficial, and some are not. The most important targets are the CNS and the gastrointestinal system, but the cardiovascular, pulmonary, genitourinary, and immune systems are all directly affected.[5]

1. McCaffery M, Portenoy RK. Overview of three groups of analgesics. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby,

1999:165-166.

2. Portenoy RK. Basic mechanisms. In: Portenoy RK, Kanner RM (eds.) *Pain management: theory and practice*. Philadelphia: FA Davis Company, 1996:249-276.
3. Pasternak GW. Pharmacological mechanisms of opioid analgesics. *Clin Neuropharmacol* 1993;16:1-18.
4. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Limbird LM (eds.) *Goodman & Gilman's the pharmacological basis of therapeutics*, 9th ed. New York: McGraw-Hill, 1996:521-555.
5. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1689-1691.



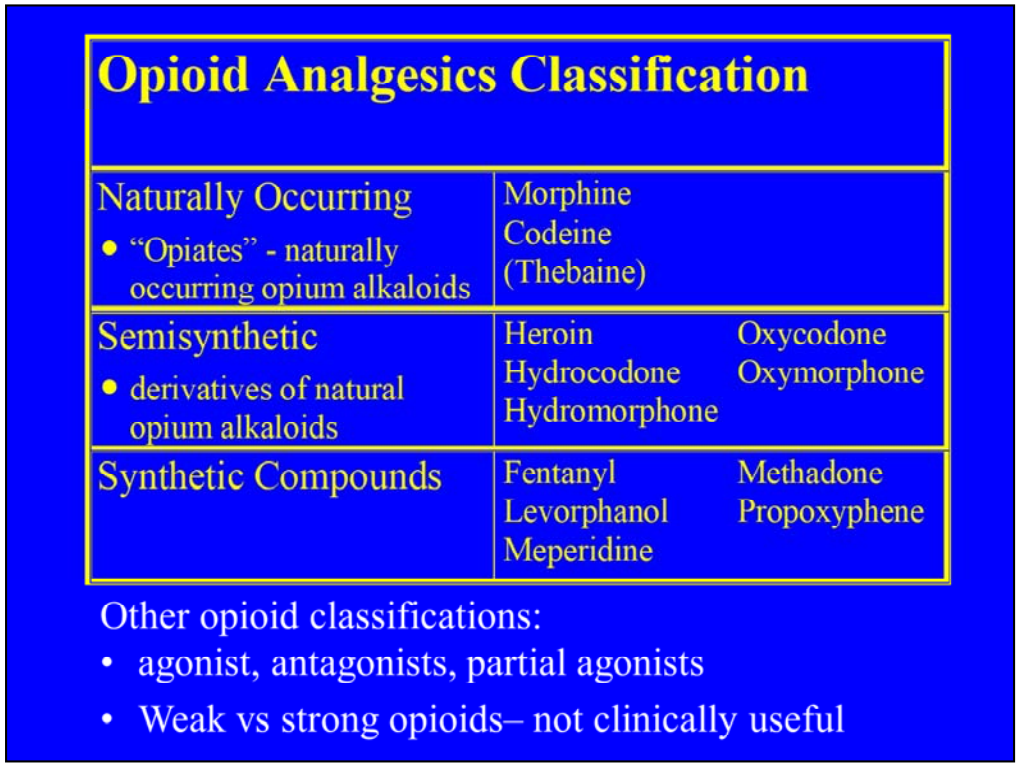
Opioids are indicated for the treatment of many different types of pain, including acute post-operative pain, moderate to severe pain, and cancer pain. While the use of opioids for chronic non-malignant pain has been debated **[linda should we use this statement??],** there have been several organizations which have supported their use in selected patients. Recently the American Academy of Pain Medicine and the American Pain Society released a joint statement which supported the use of opioids in selected patients with chronic non-malignant pain. The Federation of State Medical Boards' Model Guidelines also recognize that opioids are essential for the treatment of acute and chronic pain, whether due to cancer or non-cancer origins. [1,2]

The World Health Organization (WHO) three-step analgesic ladder, which was developed for treatment of cancer pain, provides a rational basis for developing both chronic and acute pain regimens. [3,4]

1. American Academy of Pain Medicine, American Pain Society: The use of opioids for the treatment of chronic pain: a consensus statement from the American Academy of Pain Medicine and the American Pain Society, Glenview, IL, 1997
2. Model Guidelines for the Use of Controlled substances for the Treatment of Pain, Federation of State Medical Boards of the United States, Inc., Euless, TX,

May 1998

3. Cancer Pain Relief, 2nd ed. Geneva, World Health Organization, 1996
4. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 4th ed., American Pain Society, 1999



This table outlines the various classifications of opioid analgesics.

The term "opiate" describes any naturally occurring substance that binds to opioid receptors. The term opioids refers to medications with morphine-like activity acting on mu, delta, kappa receptors. Opioids include opiates, semi-synthetic and synthetic analgesics.[1]

Opiates are naturally occurring compounds derived from opium and include morphine, codeine and thebaine. Codeine provides analgesia since it is metabolized into morphine. Thebaine has little analgesic effect on its own, but is the precursor to a variety of semi-synthetic opioids. Hydrocodone, hydromorphone, oxycodone, oxymorphone are semisynthetic opioids derived from opioid alkaloids. Heroin is not available for clinical use in the United States. Synthetic opioids include fentanyl, methadone, levorphanol, & meperidine. [2]

Another classification system considers opioids for their agonist, partial agonist, and antagonist activities at the opioid receptors. Another system subdivides them into weak or strong opioids, but this classification is of little clinical usefulness. [2]

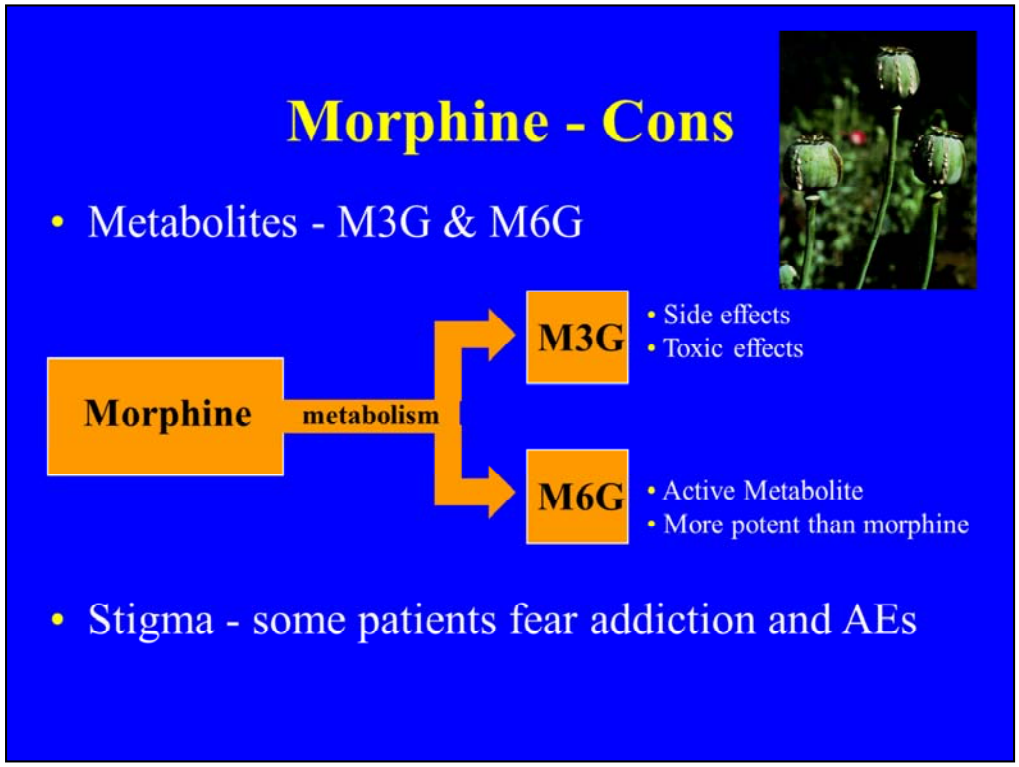
1. McCaffery M, Pasero C. *Pain: Clinical manual*, 2nd ed., p 104, St. Louis: Mosby, 1999.
2. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed., p1695-6, 1698-9. Philadelphia: Lippincott Williams & Wilkins, 2001.

The mu agonist morphine is the standard with which all other opioid drugs are compared.[1]

Morphine is the most commonly used opioid for moderate to severe pain because of its availability in a wide variety of dosage forms, its well-characterized pharmacokinetics and pharmacodynamics, and its relatively low cost.[2]

The preferred drug for intraspinal infusion continues to be morphine, but many others are used empirically.[3]

1. McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:180-181.
2. Jacox A, Carr DB, Payne R, et al. *Management of cancer pain. Clinical practice guideline* No. 9. AHCPR Publication No. 94-0592. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. March 1994:50.
3. Portenoy RK. *Contemporary diagnosis and management of pain in oncologic and AIDS patients*, 3rd ed. Newtown, PA: Handbooks in Health Care Co. 2000:99-100.

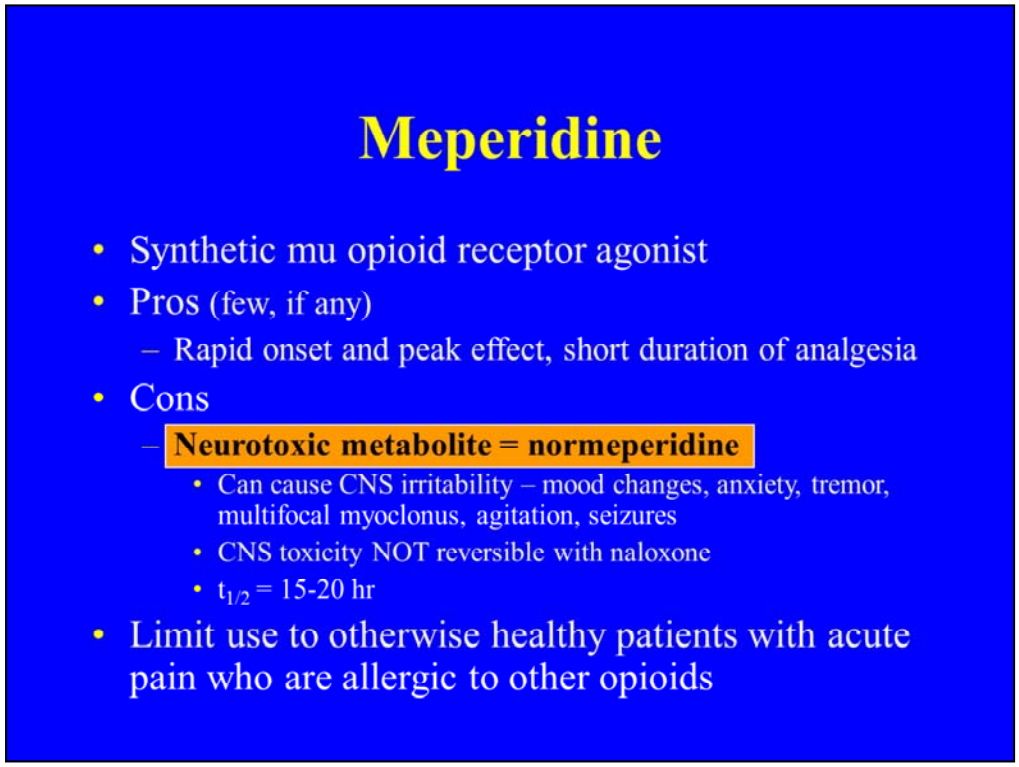


Morphine is metabolized in the liver and possibly also in the brain and kidneys. There are two major metabolites, morphine-3-glucuronide and morphine-6-glucuronide, which are mainly eliminated in urine and bile. It appears that although glucuronides are normally thought to be inactive, morphine-6-glucuronide is actually more potent than the parent compound. Morphine-3-glucuronide may have a part in the side effects of morphine. In patients with impaired renal function the accumulation of these metabolites becomes important, causing first increased effect and then, as more drug accumulates, toxic effects.[1,2]

Some patients or families view morphine as a last resort, and have an irrational fear of addiction and adverse events. The use of morphine may have special meaning to a patient or family. It may be interpreted that the patient is close to death when in fact the patient may not be.[3]

1. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1696.
2. Ruiz-López R. Continuous care of cancer pain patients. In: Aronoff GM (ed.) *Evaluation and treatment of chronic pain*, 3rd ed. Baltimore: Williams & Wilkens, 1999:392.

3. Goldstein ML. Cancer-related pain. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:541.



Meperidine continues to be the most widely used opioid analgesic for the management of pain in spite of sufficient evidence that it is not appropriate as a first-line opioid analgesic for the management of any type of pain.[1]

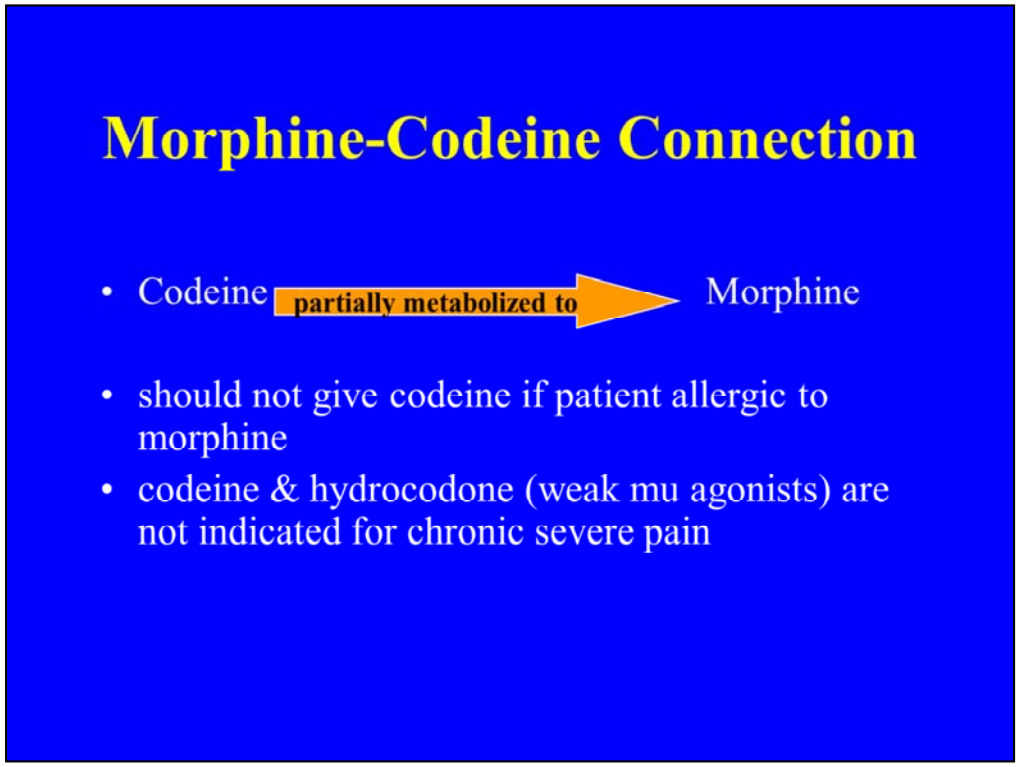
The appeal of meperidine may be in its rapid onset of action and peak effect and short duration of action.[1]

A major drawback to the use of meperidine is its active metabolite, normeperidine. Normeperidine is a CNS stimulant and can produce irritability, tremors, muscle twitching, jerking, agitation, and seizures. Normeperidine has a half-life of 15 to 20 hours compared with meperidine's half-life of 3 hours.[1,3,4]

Because normeperidine is eliminated by the kidneys, meperidine should not be used in patients with decreased renal function.[1]

The most appropriate candidates for meperidine use are patients with acute pain who are otherwise healthy and are allergic to other opioids, such as morphine and hydromorphone, or have demonstrated a more favorable outcome with meperidine than other opioid drugs.[2]

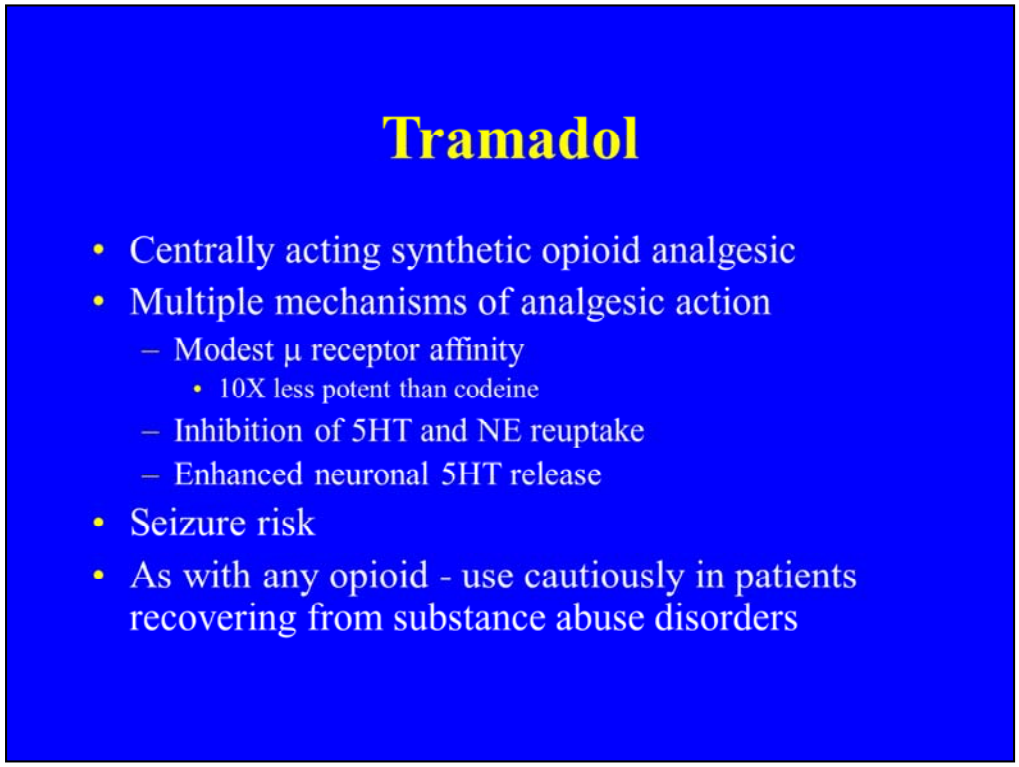
1. Pasero C, Portenoy RK, McCaffery M. Opioid analgesics. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:183-185.
2. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1700.
3. Acute Pain Management Guideline Panel. *Acute pain management: operative or medical procedures and trauma. Clinical practice guideline.* AHCPR Pub. No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. Feb. 1992.
4. Jacox A, Carr DB, Payne R, et al. *Management of cancer pain. Clinical practice guideline* No. 9. AHCPR Publication No. 94-0592. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. March 1994.



Codeine's analgesic effect comes from it being partially metabolized to morphine. Therefore, patients allergic to morphine should not receive codeine. Some patients lack the enzyme to convert codeine to morphine; thus codeine may have no analgesic properties for such individuals. [1]

Codeine & hydrocodone, being weak mu agonists, are not indicated for chronic severe pain. [1] Codeine is frequently prescribed at a dosage of 30-60 mg every 4-6 hours. An increased number of opioid side effects follow dosage increases above this level. [2]

1. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed., p 1698, 1701-2, Philadelphia: Lippincott Williams & Wilkins, 2001.
2. Acute Pain Management Guideline Panel. Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline. AHCPR Pub. No.92-0032. p 28. Rockville, MD; Agency for Health Care Policy & Research. Public Health Service, U.S. Department of Health and Human Services. Feb. 1992



Tramadol is a centrally acting synthetic analgesic with a modest affinity for mu receptors and a weak affinity for kappa and delta receptors. Tramadol is approximately 10-fold less potent in binding to the mu receptor than is codeine.[1]

Tramadol is unique in that it has both opioid and nonopioid analgesic mechanisms. In addition to the binding of opioid receptors, tramadol also inhibits serotonin and norepinepherine reuptake and enhances neuronal serotonin release, which may potentiate descending inhibitory pain pathways.[1,2]

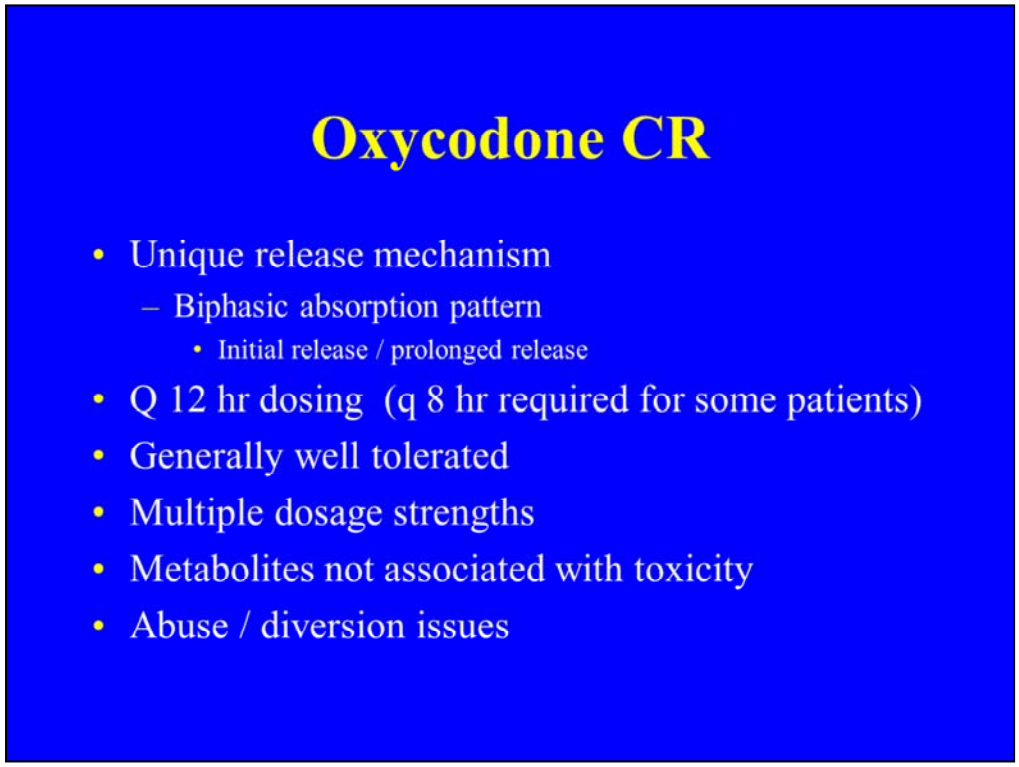
Seizures have been identified as a risk associated with the use of tramadol. It has been suggested that the occurrence of convulsions may be increased with doses of tramadol above the recommended dosing range (maximum 400mg/day), but seizures have also been reported at doses within the recommended range.[1,2]

Because tramadol is not a scheduled drug, clinicians may not be aware that it has opioid effects. Like other opioids, it should be used cautiously in persons who are recovering from substance abuse disorders.[2,3]

1. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed.

Philadelphia: Lippincott Williams & Wilkins, 2001:1704.

2. Pasero C, Portenoy RK, McCaffery M. Opioid analgesics. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:190-191.
3. Ultram® (package insert). Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc., December 1999.

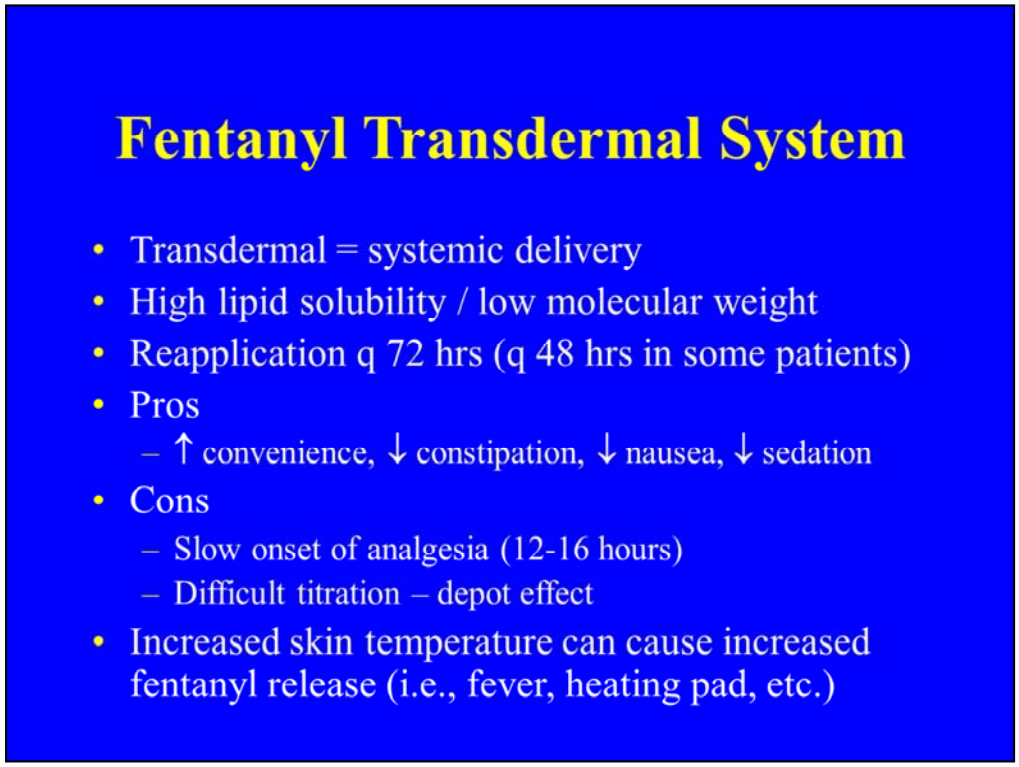


Oxycodone is currently the only opioid analgesic besides morphine that is available in the US in 12-hour controlled release form (OxyContin®) for twice daily dosing. OxyContin® is available as 10, 20, 40, and 80 mg tablets.

The release mechanism of OxyContin® differs from that of MS Contin®. OxyContin tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.[2]

Abuse and diversion issues involving controlled release oxycodone have recently become a focus for the Office of National Drug Control Policy.[3]

1. Pasero C, Portenoy Rk, McCaffery M. Opioid analgesics. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:198-199.
2. OxyContin® (package insert). Stamford, CT: Purdue Pharma L.P., November 2000.
3. Executive Office of the President. Special topic: synthetic opioids. In: *Pulse check. Trends in drug abuse. January-June 2001 reporting period*. Washington, D.C.: Office of National Drug Control Policy, November 2001:89-98.



Fentanyl is the first opioid available by the transdermal route. Its low molecular weight and high lipophilicity make it a good candidate for transdermal administration. The transdermal systems are designed to release fentanyl at a nearly constant rate along a concentration gradient from patch to skin.[1,2]

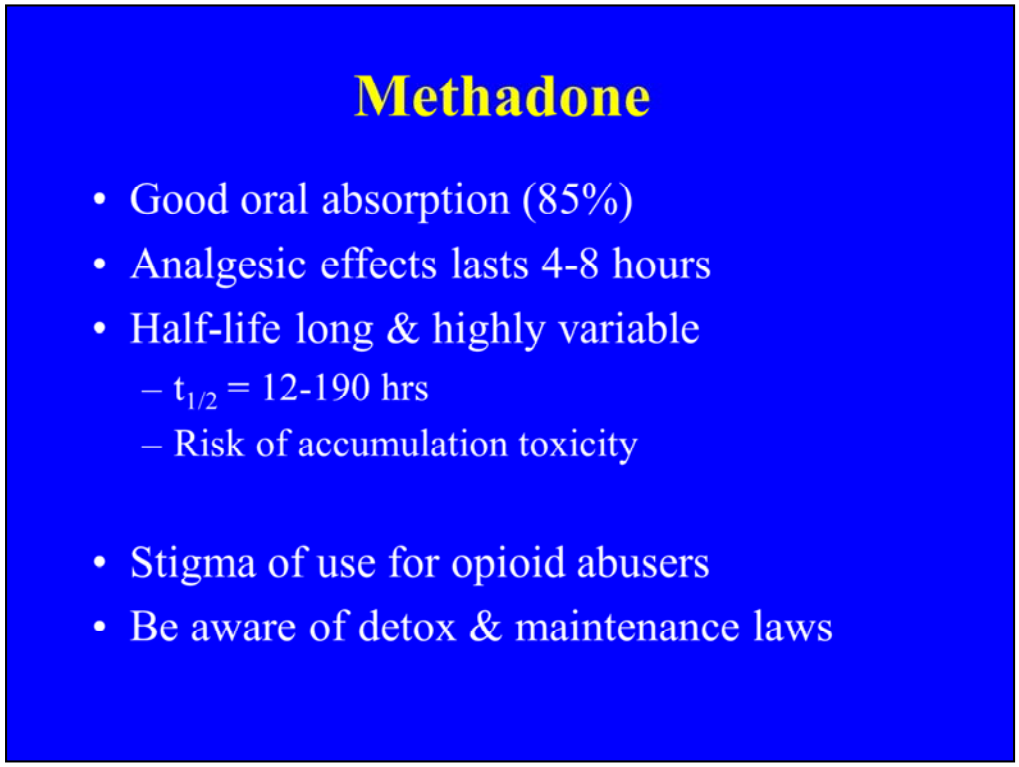
The life of the transdermal fentanyl patch is approximately 72 hours, although some patients may require a new patch every 48 hours.[2]

Transdermal fentanyl gives the same degree of pain control as morphine but is associated with significantly less constipation, nausea, and daytime drowsiness.[1]

A major drawback to the use of transdermal fentanyl is that it takes 12 to 16 hours for substantial analgesic effect to be experienced by the patient once dosing begins, and titration to an effective dose may require days, necessitating the addition of an opioid by an alternate route during this period. Another disadvantage to the transdermal system is that it does not allow for easy dose adjustment in the management of side effects. If the patch is removed because of adverse effects, a depot of fentanyl remains and serum concentrations decline very slowly, falling about 50% in approximately 17 hours.[2]

Transdermal fentanyl absorption also may be increased by either external or internal sources of heat. Care must be taken when using the transdermal route in febrile patients. Drug absorption by the transdermal route is influenced by elevated temperature; a temperature of 104° F can cause serum fentanyl concentration to increase by one-third, necessitating monitoring for side effects and adjustment of dose. Patients should also be cautioned against taking excessively hot showers. Sleeping in a heated waterbed or putting a heating pad over the patch will also increase the amount of fentanyl being absorbed.[2,3]

1. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1700-1701.
2. Pasero C, Portenoy RK, McCaffery M. Opioid analgesics. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:206-209.
3. Duragesic® (Package insert). Titusville, NJ: Janssen Pharmaceutica, January 2000.

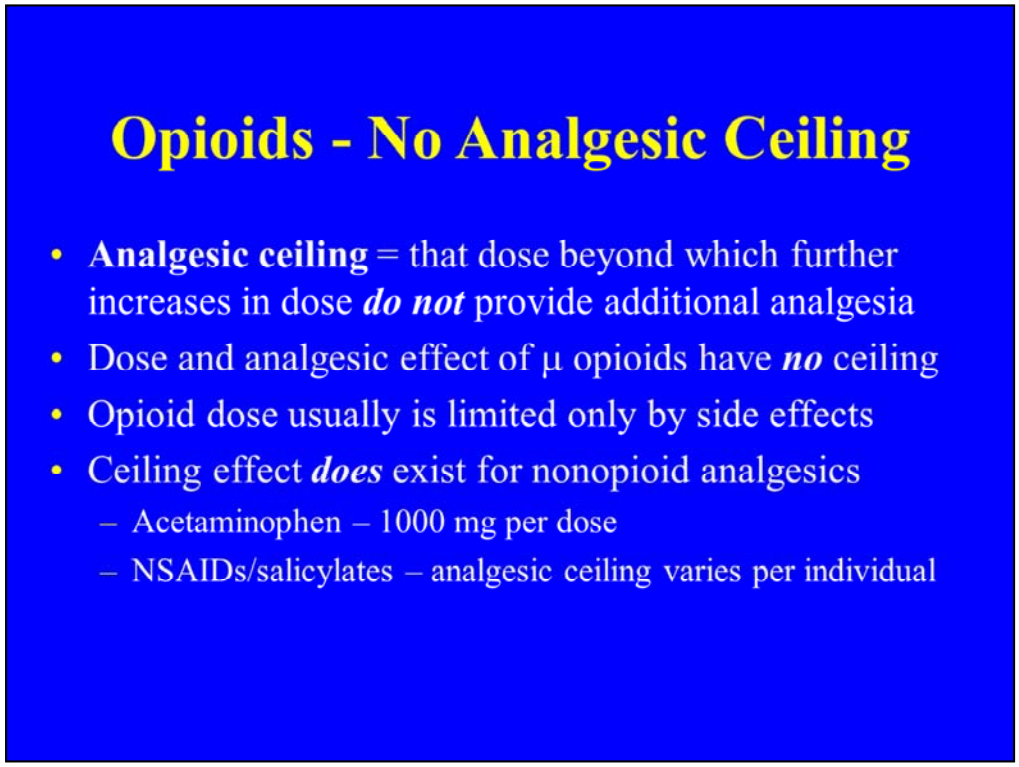


Methadone is an effective medication for chronic pain, however it's pharmacokinetics are complex. It is well-absorbed, with an oral bioavailability of 85%. Its analgesic effects last 4 to 8 hours, but it's half-life is much longer and highly variable (12-190 hours). There is therefore there is a risk of accumulation of toxic levels as you are trying to reach analgesic steady state. [1,2,3]

Given the fact that methadone can be used both as an analgesic and as a treatment for opioid addiction (detoxification/maintenance), clinicians should be aware of federal regulations regarding its use. The use of methadone for management of opioid addiction requires a specific federal license; when used as an analgesic, no special license is required. [1] As with conventional medical practice, appropriate documentation and monitoring is, of course, very appropriate. Because of its use for treatment of opioid addiction, there is also the potential that patients or family members may be mistakenly interpret that the patient is a drug abuser. [2]

1. Aronoff GM, Gallagher RM. Pharmacological Management of Chronic Pain: a review. In Aronoff GM Evaluation and Treatment of Chronic Pain, 3rd ed, p 441, 446. Williams & Wilkens, Baltimore, 1999.

2. McCaffery M, Pasero C. *Pain: Clinical manual*, 2nd ed., p 179, 185, 541, St. Louis: Mosby, 1999.
3. Portenoy RK: Opioid analgesics. In Portenoy RK, Kanner RM, editors: Pain Management, Theory and Practice, pp249-276, Philadelphia, 1996, FA Davis



The definition of 'analgesic ceiling' is outlined on this slide.[1]

The dose and analgesic effect of mu agonist opioids have no ceiling. However, other analgesics do exhibit a ceiling effect, whereby increasing the dose of the agent does not provide additional analgesia but may cause additional side effects.[1]

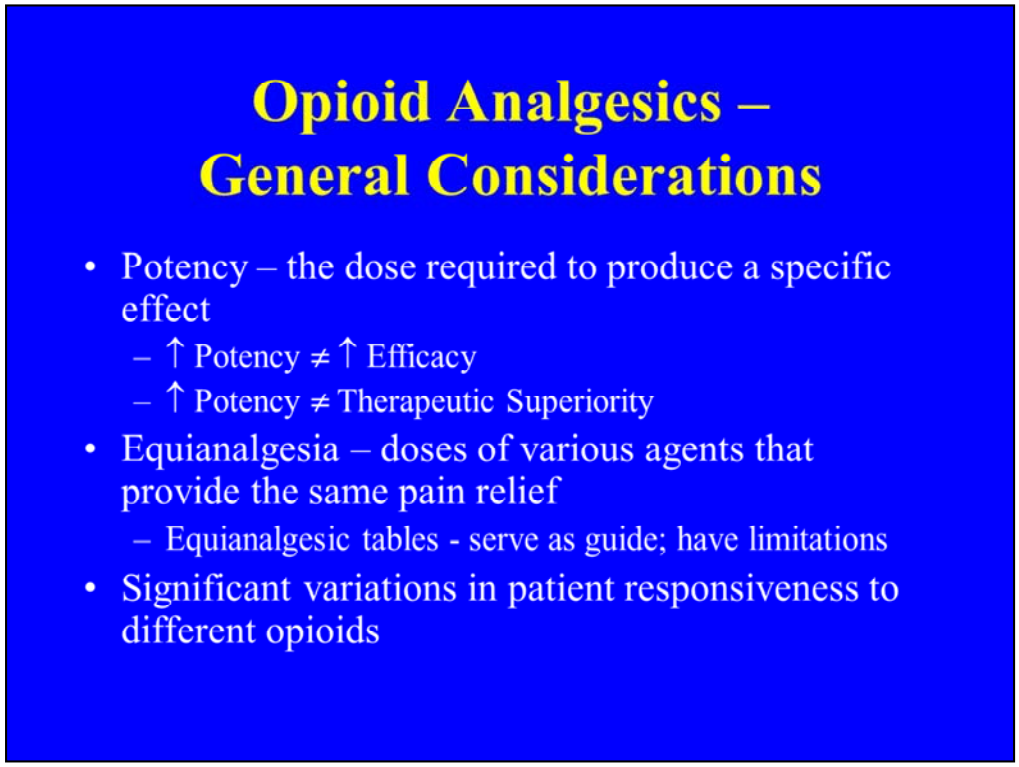
There is a ceiling on the analgesia of acetaminophen - increasing each dose greater than 1000 mg will result in very little added analgesia. There is also a ceiling to the analgesia of each NSAID, but it varies from one person to another.[2,3]

In older patients, the chronic use of NSAIDs is associated with a high frequency of adverse effects. The risk of gastrointestinal bleeding associated with NSAID use in a general population is about 1%. For those aged 60 or older, the risk reaches 3 to 4%, and for those aged 60 or older with a history of gastrointestinal bleeding, the risk is about 9%.[4]

1. Pasero C, Portenoy RK, McCaffery M. Opioid analgesics. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:162,170.
2. McCaffery M, Portenoy RK. Nonopioids. In: McCaffery M, Pasero C. *Pain:*

clinical manual, 2nd ed. St. Louis: Mosby, 1999:141.

3. Sunshine A, Olsen NZ. Nonnarcotic analgesics. In: Wall PD, Melzack R (eds.) *Textbook of pain*, 3rd ed., New York: Churchill Livingstone, 1994:923-942.
4. AGS Panel on Chronic Pain in Older Persons. The management of chronic pain in older persons. *J Am Geriatr Soc* 1998;46(5):635-651.

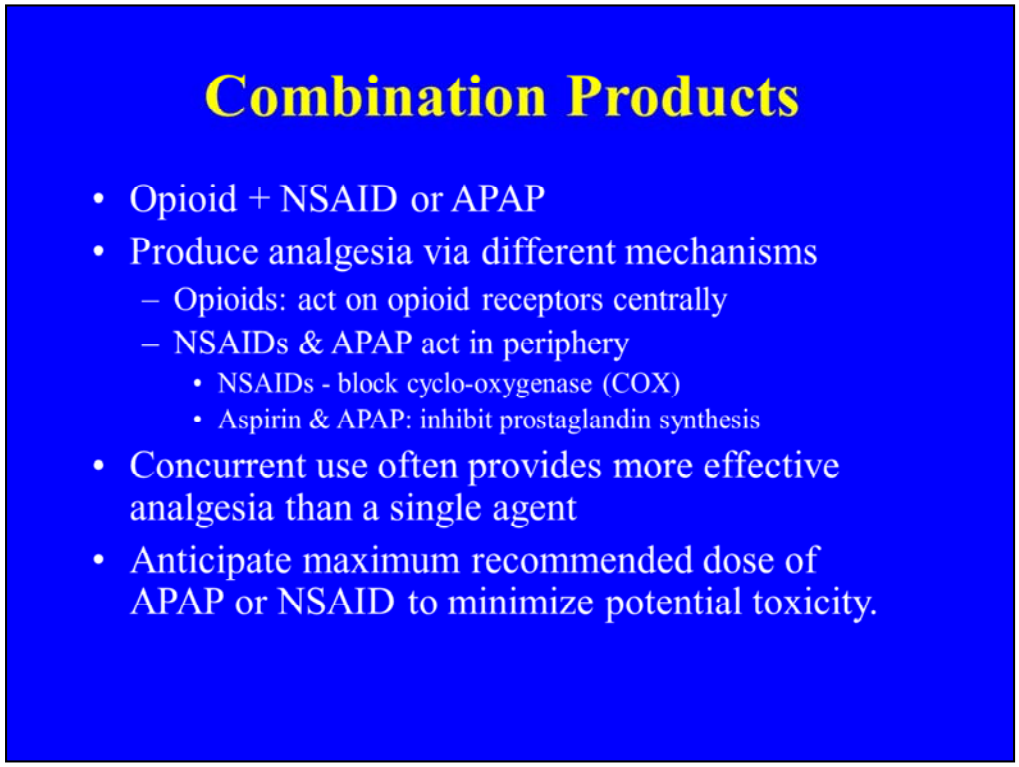


Potency refers to the power of a medicinal agent to generate its desired outcome, that is, the dose required to produce a specific effect. Relative analgesic potency, or the ratio of doses to produce an equivalent degree of anesthesia, is the basis for the equianalgesic dose table. Equianalgesia refers to different doses of two agents that provide approximate pain relief. [1]

A common misconception is that the more potent a drug is, the more therapeutically superior it is. In reality, all opioid analgesics are capable of producing the same degree of analgesia if doses are appropriately adjusted. Increased potency alone does not provide any advantage because the more potent drugs also exhibit a parallel increase in their ability to produce undesirable effects. [2] Significant interindividual and intraindividual variations exists in patients' responsiveness to opioid analgesics. For example, with the same opioid, one patient may achieve excellent analgesia with few side effects, whereas another patient experiences intolerable side effects with minimal or no analgesia. [2,3]

Several equianalgesic tables have been published. It is important to recognize that these tables are meant to serve only as a guide for conversion between agents. Much of the information in these tables was derived from single dose studies and therefore may have limitations in applicability to repetitive administration. [1]

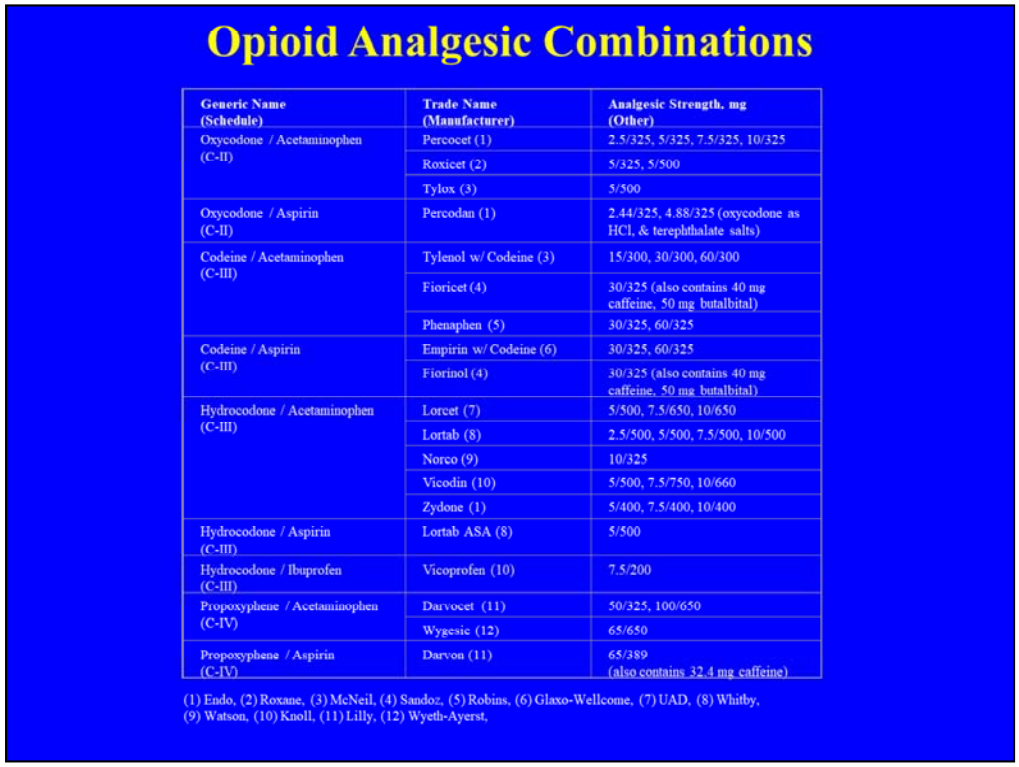
1. Anderson RA et al. Accuracy in equianalgesic dosing: conversion dilemmas. J Pain Sympt Management 2001;21:397-406
2. McCaffery M, Pasero C. *Pain: Clinical manual*, 2nd ed., p 170-1, 185, 541, St. Louis: Mosby, 1999.
3. Portenoy RK: Opioid analgesics. In Portenoy RK, Kanner RM, editors: Pain Management, Theory and Practice, pp249-276, Philadelphia, 1996, FA Davis



Opioid analgesics are sometimes combined with acetaminophen (APAP) or a nonsteroidal anti-inflammatory (NSAID) medication such as aspirin or ibuprofen. The rationale for this strategy is the enhancement of efficacy by combining 2 analgesics with different mechanisms of action. Opioid analgesics work in the central nervous system, while aspirin, NSAIDs and acetaminophen (APAP) work peripherally . Acetaminophen has analgesic and antipyretic effects similar to aspirin – working by inhibiting prostaglandin synthesis. In addition APAP also has been found to have central analgesic properties. NSAIDs exert their anti-inflammatory effect and analgesic actions by blocking the cyclo-oxygenase (COX) pathway at the site of tissue injury in the periphery. [1,2]

There is reasonable evidence that these combination regimens often provide more effective analgesia than either of the drug classes alone. [1,3] With the fixed-dose combinations, it is also important to anticipate the maximum recommended dose of acetaminophen or NSAID in order to avoid potential toxicity. [4]

1. Beaver WT Nonsteroidal Anti-Inflammatory analgesics and their combinations with opioids. In Aronoff GM Evaluation and Treatment of Chronic Pain, 3rd ed, p 455-6, 466-7, Williams & Wilkens, Baltimore, 1999.
2. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed., p 1667, 1674-5, Philadelphia: Lippincott Williams & Wilkins, 2001.
3. AHCPR Clinical Practice Guideline, Acute Pain Management: Operative Medical Procedures and Trauma, Feb 1992, p 16
4. AGS Panel on Chronic Pain in Older Persons. Clinical Practice Guidelines. The Management of Chronic Pain in Older Persons. J Am Ger Soc 1998; 46: 635-651



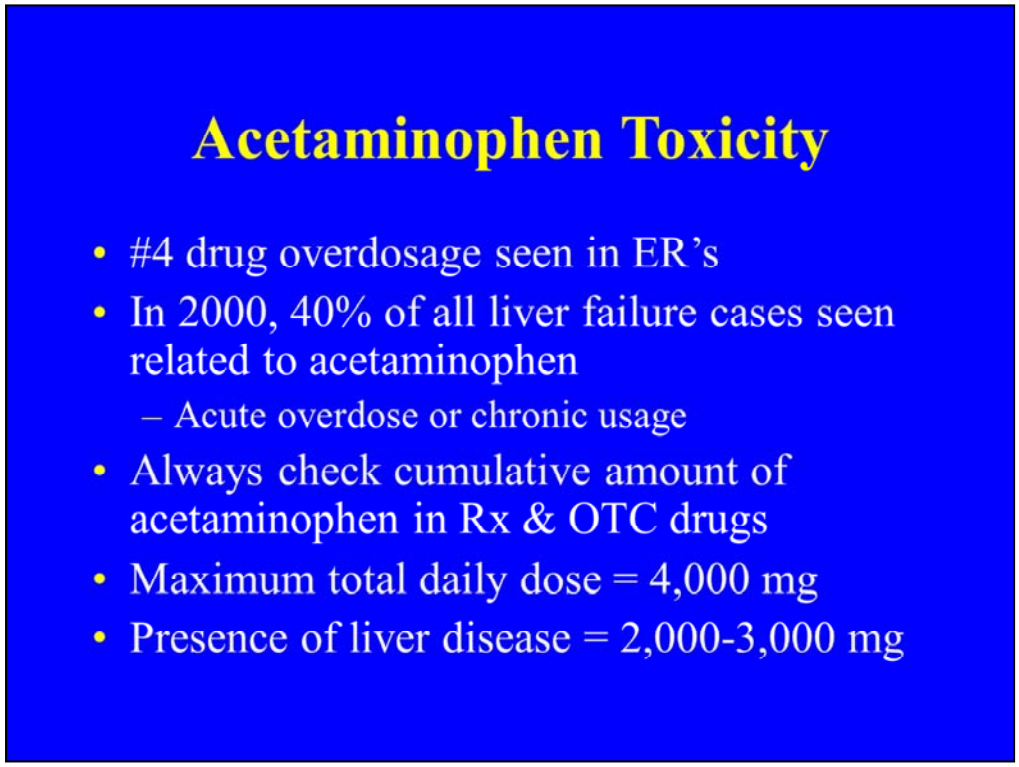
Opioid Analgesic Combinations

Generic Name (Schedule)	Trade Name (Manufacturer)	Analgesic Strength, mg (Other)
Oxycodone / Acetaminophen (C-II)	Percocet (1)	2.5/325, 5/325, 7.5/325, 10/325
	Roxicet (2)	5/325, 5/500
	Tylox (3)	5/500
Oxycodone / Aspirin (C-II)	Percodan (1)	2.44/325, 4.88/325 (oxycodone as HCl & terephthalate salts)
Codeine / Acetaminophen (C-III)	Tylenol w/ Codeine (3)	15/300, 30/300, 60/300
	Fioricet (4)	30/325 (also contains 40 mg caffeine, 50 mg butalbital)
	Phenaphen (5)	30/325, 60/325
Codeine / Aspirin (C-III)	Empirin w/ Codeine (6)	30/325, 60/325
	Fiorinol (4)	30/325 (also contains 40 mg caffeine, 50 mg butalbital)
Hydrocodone / Acetaminophen (C-III)	Lorcet (7)	5/500, 7.5/650, 10/650
	Lortab (8)	2.5/500, 5/500, 7.5/500, 10/500
	Norco (9)	10/325
	Vicodin (10)	5/500, 7.5/750, 10/660
	Zydone (1)	5/400, 7.5/400, 10/400
Hydrocodone / Aspirin (C-III)	Lortab ASA (8)	5/500
Hydrocodone / Ibuprofen (C-III)	Vicoprofen (10)	7.5/200
Propoxyphene / Acetaminophen (C-IV)	Darvocet (11)	50/325, 100/650
	Wygesic (12)	65/650
Propoxyphene / Aspirin (C-IV)	Darvon (11)	65/389 (also contains 32.4 mg caffeine)

(1) Endo, (2) Roxane, (3) McNeil, (4) Sandoz, (5) Robins, (6) Glaxo-Wellcome, (7) UAD, (8) Whitby, (9) Watson, (10) Knoll, (11) Lilly, (12) Wyeth-Ayerst,

This chart lists some of the common opioid analgesic combinations by generic and trade name, and the various strengths of the opioid & non-opioid (acetaminophen, aspirin, NSAID) analgesic in each. [1,2]

1. Drug Facts and Comparisons, Jan 2000, p 803-806. Facts and Comparisons. St. Louis, MO
2. Percocet ® (package insert), Chadds Ford, PA, Endo Pharmaceuticals Inc. August 2001

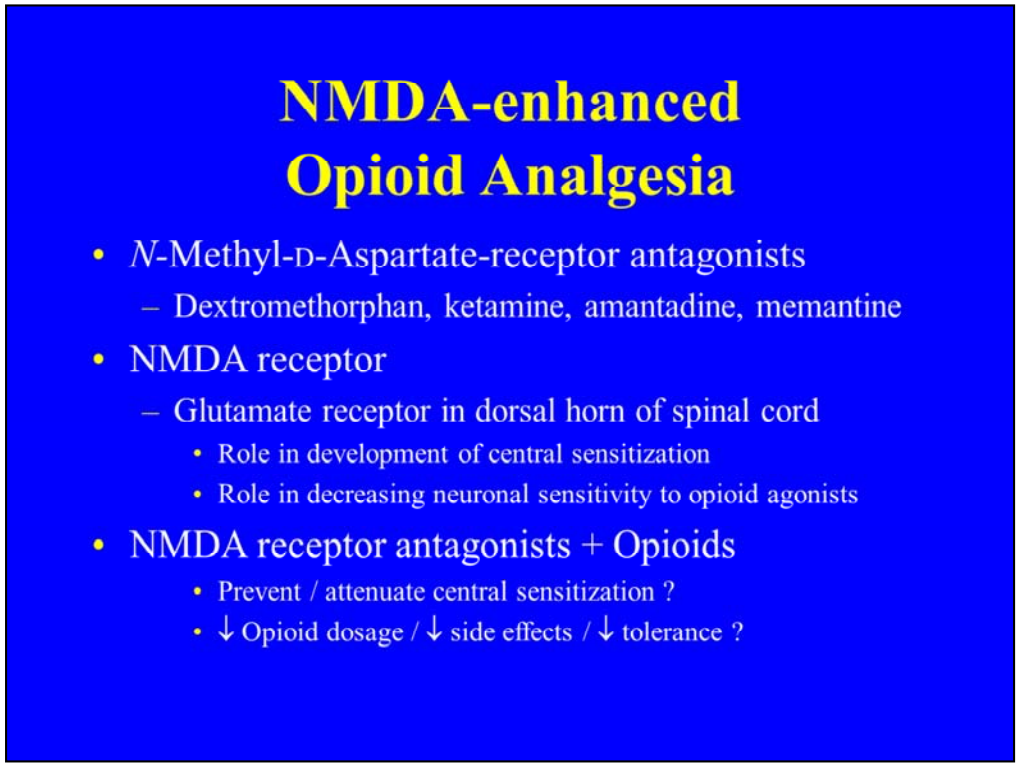


REFS FOR FIRST 2 BULLETS AND DOSE IN HEPATIC DISEASE (LAST BULLET)????

With acetaminophen, toxic effects are rarely seen in individuals who adhere to recommended therapeutic doses, which are limited to a maximum of 4 g per day.[1]

The mechanism for damage by acetaminophen is through a highly reactive metabolite that normally is inactivated by glutathione. Overdoses of acetaminophen deplete glutathione stores, allowing the metabolite to accumulate and bind covalently to cell constituents. In severe cases, the result may be acute hepatic necrosis, which can progress to fulminant liver failure.[1]

1. Miyoshi HR. Systemic nonopioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1675-1676.



Excitatory amino acids, such as glutamate and aspartate, are released by primary afferent neurons in response to noxious stimuli and are important in the central processing of pain-related information. Interactions at the NMDA receptor are involved in the development of central nervous system changes that may underlie chronic pain and modulate opioid mechanisms, specifically tolerance.[1,2]

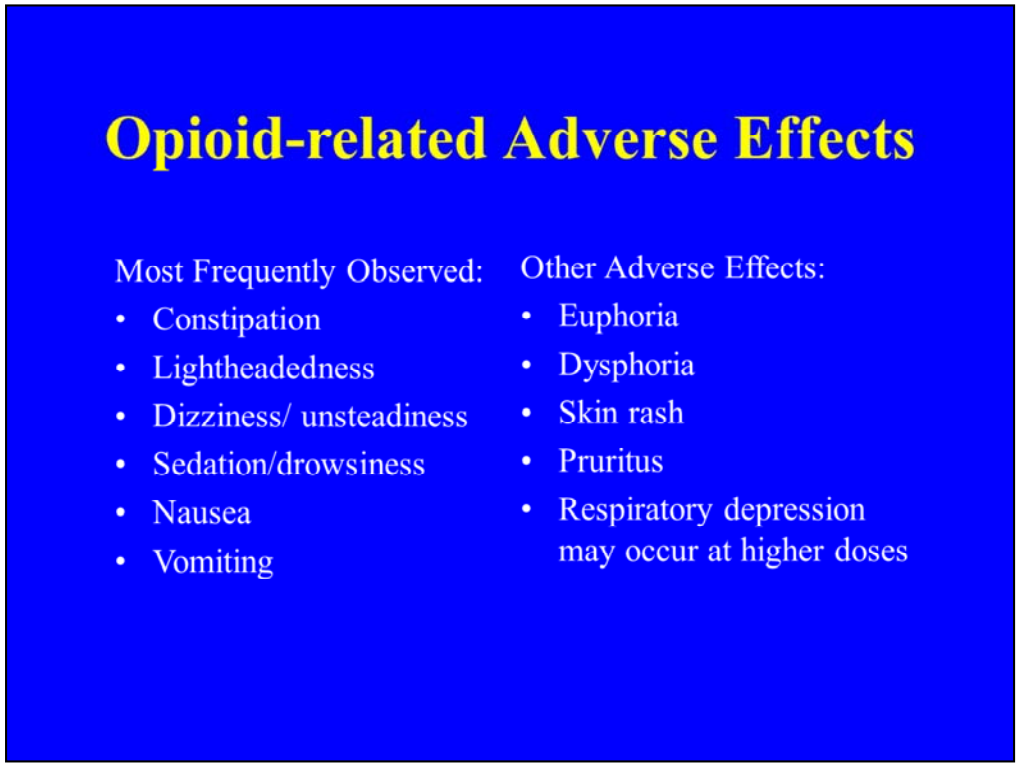
Preclinical studies have established that the NMDA receptor is involved in the sensitization of central neurons after injury and the development of the 'wind-up' phenomenon, a change in the response of central neurons that has been associated with neuropathic pain.[1]

Antagonists at the NMDA receptor may offer a novel approach to the treatment of pain.[1]

The NMDA receptor in the dorsal horn of the spinal cord has now been demonstrated to play a role in the development of central sensitization and, separately, in the mechanisms underlying opioid analgesia and tolerance. Future studies will be needed to clarify the positioning of NMDA-receptor antagonists as analgesics within the broader armamentarium for pain control. There are sufficient data now to generate interest in the role they may play as

co-analgesics combined with opioids and as primary analgesics for pain, including some neuropathic pain that responds poorly to traditional analgesics.[3]

1. Portenoy RK, McCaffery M. Adjuvant analgesics. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:328-330.
2. Mao J, Price DD, Mayer DJ. Experimental mononeuropathy reduces antinociceptive effects of morphine: implications for common intracellular mechanisms involved in morphine tolerance and neuropathic pain. *Pain* 1995;61:353-364.
3. Portenoy RK, et al. NMDA-receptor antagonists: evolving role in analgesia. *J Pain Symptom Manage* 2000;19(1S):S1-S64.



Slide is modified from Slide 14 from Percocet slide kit (Acute Pain: A treatment Imperitive); incorporated info from Slide 16 from Acute Pain slide kit (Optimizing Outcomes)

The potential for opioid-related side effects should be discussed with the patient when dispensing an opioid analgesic. The most common adverse effects associated with the use of opioid analgesics are listed on this slide. **(VERBAGE FROM**

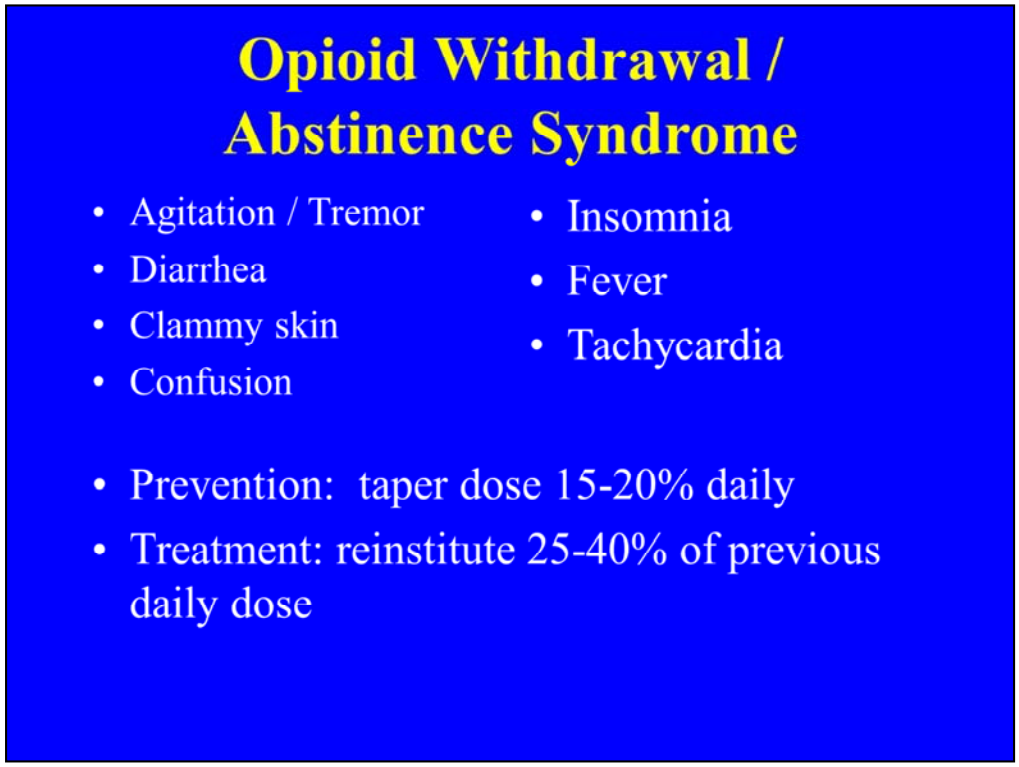
"Percocet Slide kit" "Acute Pain: A treatment Imperative")

(VERBAGE FROM OPTIMIZING OUTCOMES / ACUTE PAIN SLIDE SET):

Constipation is the most frequent and uncomfortable adverse effect associated with opioid therapy. Therefore, when initiation therapy, institute anti-constipation efforts such as cathartics, stool softeners and fluids as needed. CNS side effects such as sedation, drowsiness, confusion, dizziness or unsteadiness can develop during initiation of opioid therapy, but ususlly clear in 3-5 days. If persistent sedation or drowsiness occur, administer concomitant amphetamine, and/or reduce the dose and increase the frequency of the opioid. [1]

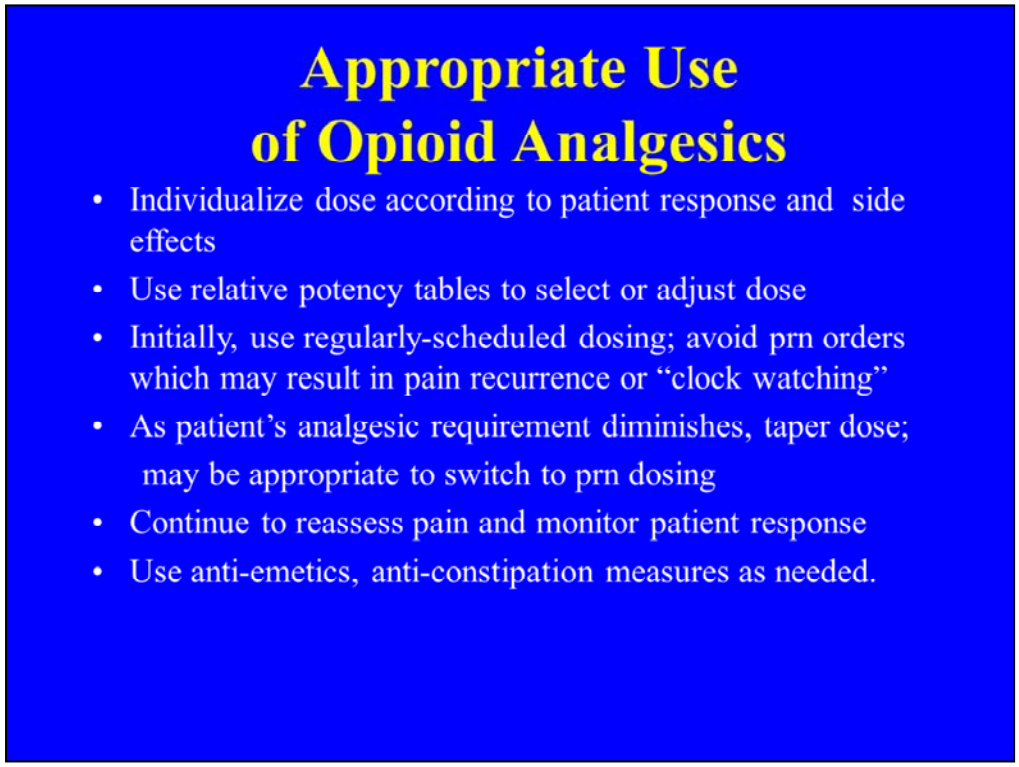
Clinically significant respiratory depression is uncommon in patients experiencing pain provided the dose of the opioid analgesic is titrated to obtain proper pain relief. [1] This complication will occur, however, when opioids are given in excessive doses or when adequate doses are administered too frequently. [1] To terminate mild respiratory depression, reduce the opioid dosage. Moderate or severe respiratory depression should be treated with naloxone. [1] (See Full Prescribing Information for details)

1. Bonica JJ (1990). General considerations of acute pain. In:Bonica, JJ (ed.), The Management of Pain (pp 159-179). Philadelphia: Lea & Febiger.



Abrupt discontinuation, precipitous dose reduction, or the administration of an opioid antagonist or agonist-antagonist can precipitate a withdrawal or abstinence syndrome. This syndrome consists of yawning, lacrimation, sneezing, agitation, tremor, confusion, insomnia, fever, tachycardia, and other signs of sympathetic nervous system hyperexcitability. This syndrome can be prevented by tapering the dose by 15-20% daily, or treated by reinstituting 25-40% of the previous daily dose. [1]

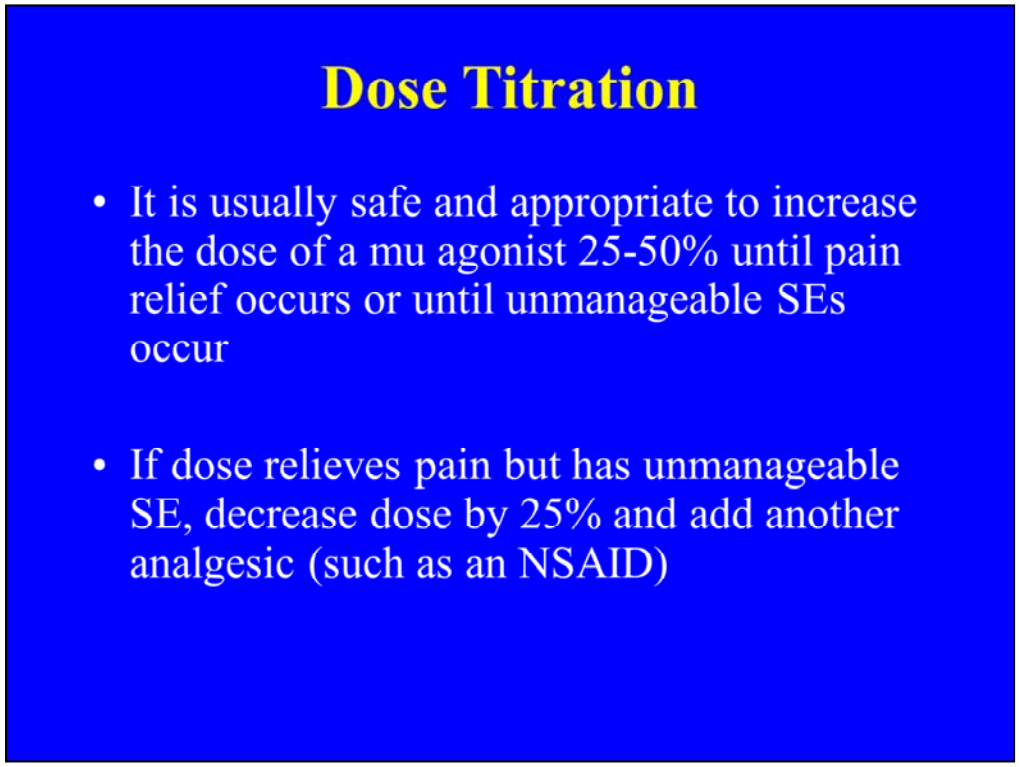
1. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed., pp 1695, Philadelphia: Lippincott Williams & Wilkins, 2001.



This is slide 19 for Optimizing Outcomes

In summary, the dose of opioid analgesic should always be individualized according to the patient's response to the medication and side effects. To avoid recurrence of pain or patient "clock watching," opioid analgesics for acute pain should initially be administered on a regularly-scheduled basis (q4h, q6h, etc.), rather than on a "prn" (as needed) basis. Late in the postoperative course, it may be acceptable to switch to an as-needed (prn) schedule as the patient's analgesic requirements diminish, provided pain is assessed at regular intervals. Finally, utilize contingency planning, such as orders to avert or treat opioid related side effects like constipation. [1]

1. AHCPR 1992



Signs that increasing the opioid dose is needed include a decreased duration of analgesia or an increase in the number of rescue doses. When a slight improvement in analgesia is needed, a 25% increase in dose may be sufficient, for a moderate effect, a 50% increase, and for a strong effect, such as for the treatment of severe pain, a 100% increase may be indicated.

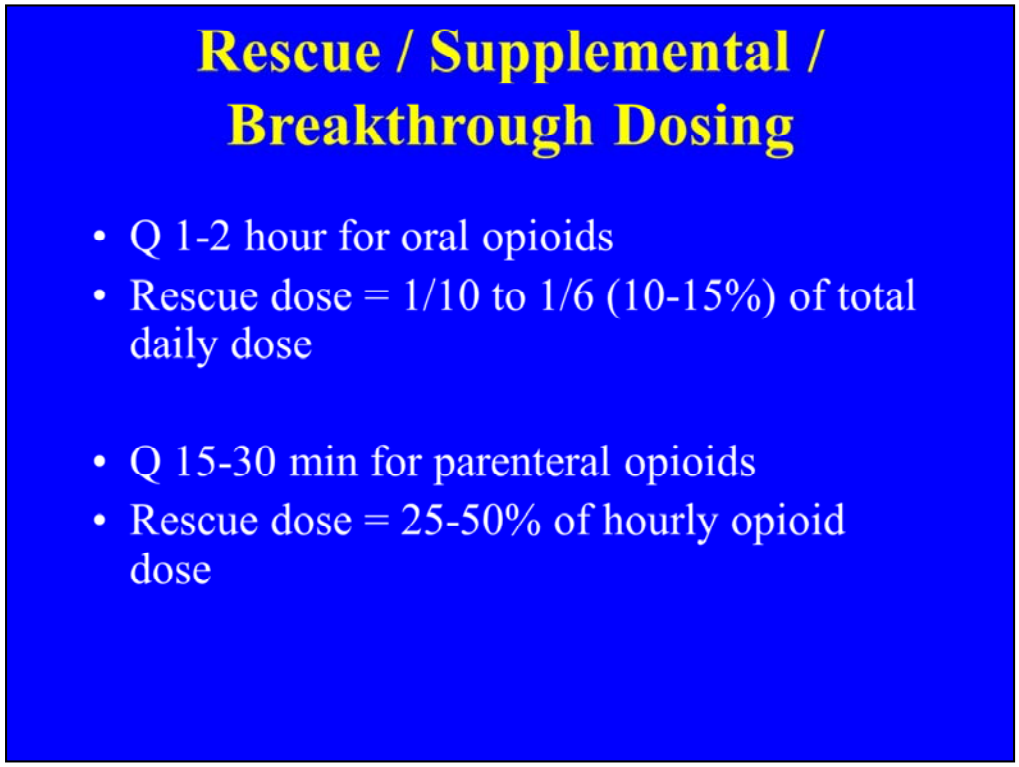
Downward titration maybe necessary if pain has subsided or there are opioid side effects; the opioid dose should be decreased by 25% if the side effect is mild, or by 50-100% for more substantial side effects.

Jacox A, Carr DB, Payne R et al. Management of cancer pain: clinical practice guideline No. 9, AHCPR Publication No. 94-0592, Rockville MD, US Public Health Service, AHCPR, March 1994

Levy MH Pharmacologic treatment of cancer pain. New Eng J Med 335(15) 1124-1132, 1996

McCaffery M, Pasero C. *Pain: Clinical manual*, 2nd ed., p 112, 179, 247, 256, 260.

St. Louis: Mosby, 1999.



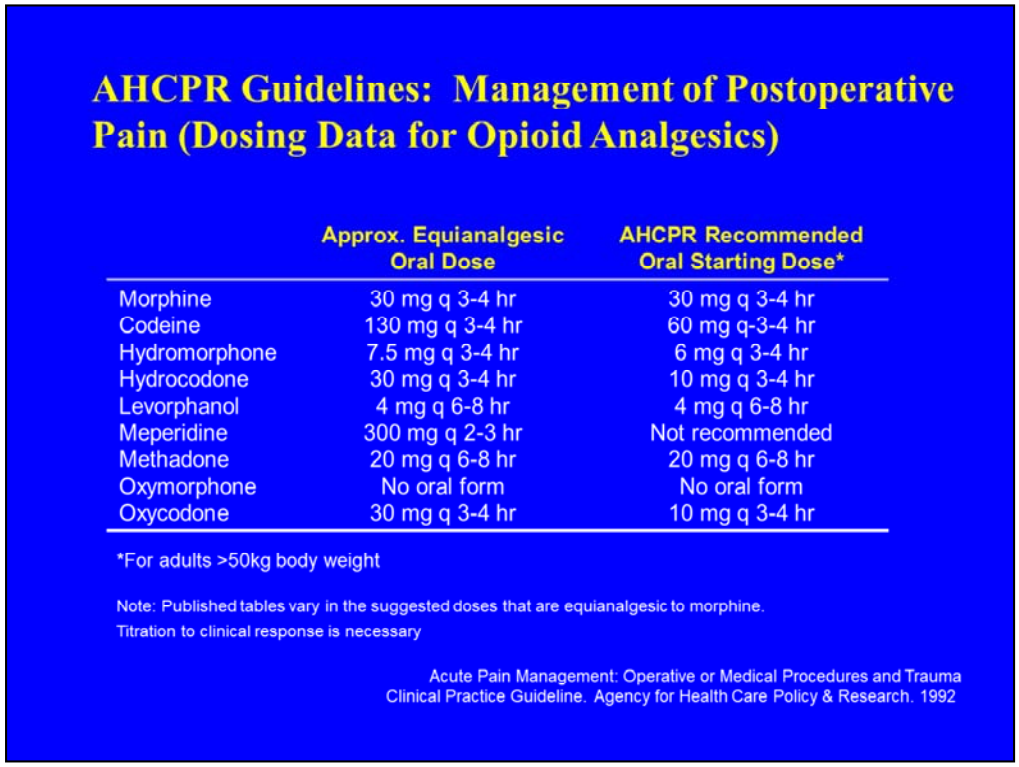
The term rescue dose can be used interchangeably with supplemental or breakthrough dose. Patients should be offered rescue doses every 1-2 hours for oral opioids and every 15-30 minutes for parenteral opioids. For patients taking oral opioids the recommended amount is between 1/6 & 1/10 of the total daily around-the-clock dose of the opioid. The recommended rescue dose for continuous parenteral or epidural opioid infusionsis 25 to 50% of the hourly opioid dose.

For patients taking oral opioids, rescue doses may be offered every 1-2 hours; the recommended amount is

between 1/10 to 1/6 (10-15%) of the total daily around-the-clock dose of the opioid. The recommended rescue dose for continuous parenteral or epidural opioid infusions is 25 to 50% of the hourly opioid dose, & may be offered every 15-30 minutes.

APS Principles of analgesic use in treatment of acute and cancer pain, ed 3, Glenview IL 1992

McCaffery M, Pasero C. *Pain: Clinical manual*, 2nd ed., p 244-5, St. Louis: Mosby, 1999.



AHCPR Guidelines: Management of Postoperative Pain (Dosing Data for Opioid Analgesics)

	Approx. Equianalgesic Oral Dose	AHCPR Recommended Oral Starting Dose*
Morphine	30 mg q 3-4 hr	30 mg q 3-4 hr
Codeine	130 mg q 3-4 hr	60 mg q-3-4 hr
Hydromorphone	7.5 mg q 3-4 hr	6 mg q 3-4 hr
Hydrocodone	30 mg q 3-4 hr	10 mg q 3-4 hr
Levorphanol	4 mg q 6-8 hr	4 mg q 6-8 hr
Meperidine	300 mg q 2-3 hr	Not recommended
Methadone	20 mg q 6-8 hr	20 mg q 6-8 hr
Oxymorphone	No oral form	No oral form
Oxycodone	30 mg q 3-4 hr	10 mg q 3-4 hr

*For adults >50kg body weight

Note: Published tables vary in the suggested doses that are equianalgesic to morphine.
Titration to clinical response is necessary

Acute Pain Management: Operative or Medical Procedures and Trauma
Clinical Practice Guideline. Agency for Health Care Policy & Research. 1992

This text and slide is from Slide 14 from Acute Pain Slide Kit (Optimizing Outcomes)

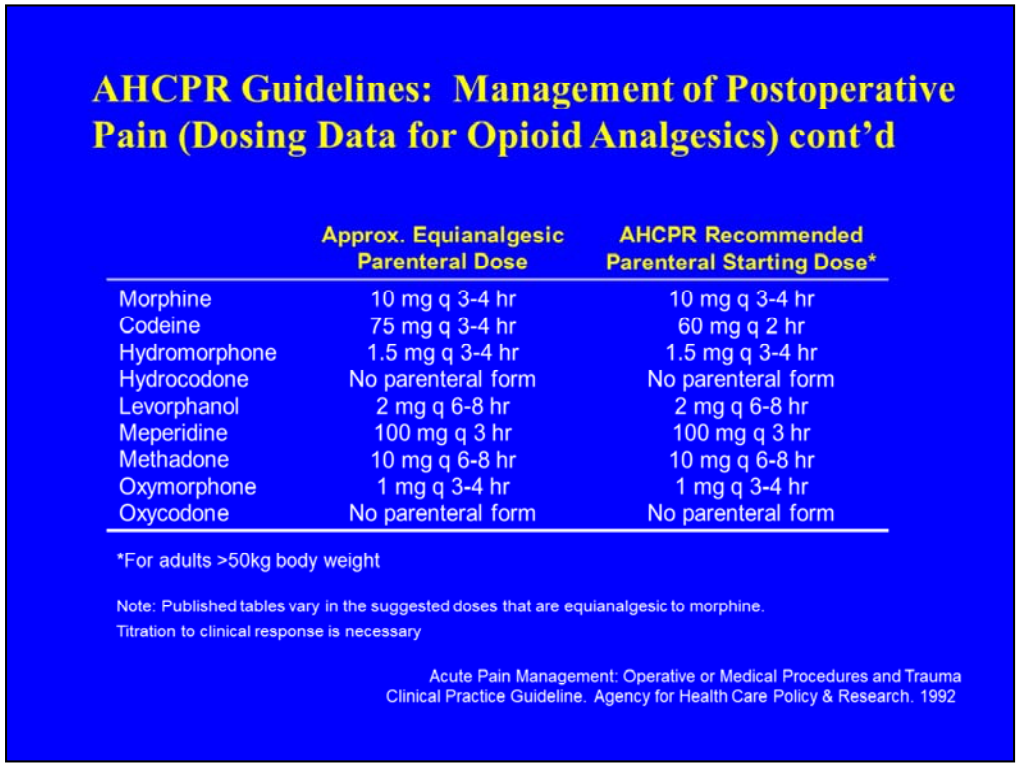
To facilitate appropriate dosing of Opioid analgesics, tables of relative potency estimates have been prepared. Published tables may vary in the suggested doses that are equianalgesic to morphine. Clinical response is the criterion that must be applied for each patient; titration to clinical response is necessary.[1]

This slide describes the approximate equianalgesic oral doses of opioid analgesics for adults >50 kg body weight referenced in the AHCPR Clinical Practice Guideline entitled Acute Pain Management: Operative or Medical Procedures and Trauma. Recommended pediatric doses and doses for adults<50 kg are lower than these doses. See full text of guideline for specific recommendations. [1]

Note: This slide reflects the AHCPR recommendations for dosing opioids. In some cases, these recommendations differ from those contained in the products' package inserts. Please consult the Full Prescribing Information for the Manufacturer's recommended dosing.

1. Acute Pain Management Guideline Panel. Acute Pain Management: Operative or

Medical Procedures and Trauma. Clinical Practice Guideline. AHCPR Pub. No.92-0032. Rockville, MD; Agency for Health Care Policy & Research. Public Health Service, U.S. Department of Health and Human Services. Feb. 1992.



AHCPR Guidelines: Management of Postoperative Pain (Dosing Data for Opioid Analgesics) cont'd

	Approx. Equianalgesic Parenteral Dose	AHCPR Recommended Parenteral Starting Dose*
Morphine	10 mg q 3-4 hr	10 mg q 3-4 hr
Codeine	75 mg q 3-4 hr	60 mg q 2 hr
Hydromorphone	1.5 mg q 3-4 hr	1.5 mg q 3-4 hr
Hydrocodone	No parenteral form	No parenteral form
Levorphanol	2 mg q 6-8 hr	2 mg q 6-8 hr
Meperidine	100 mg q 3 hr	100 mg q 3 hr
Methadone	10 mg q 6-8 hr	10 mg q 6-8 hr
Oxymorphone	1 mg q 3-4 hr	1 mg q 3-4 hr
Oxycodone	No parenteral form	No parenteral form

*For adults >50kg body weight

Note: Published tables vary in the suggested doses that are equianalgesic to morphine.
Titration to clinical response is necessary

Acute Pain Management: Operative or Medical Procedures and Trauma
Clinical Practice Guideline. Agency for Health Care Policy & Research. 1992

This text & slide is Slide 15 from Acute Pain Slide Kit (Optimizing Outcomes)

This slide references the AHCPR Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline recommendations for approximate equianalgesic parenteral doses of opioid analgesics for adults >50 kg body weight. Recommended pediatric doses and doses for adults <50 kg body weight are lower than these doses. See full text of guideline for specific recommendations. [1]

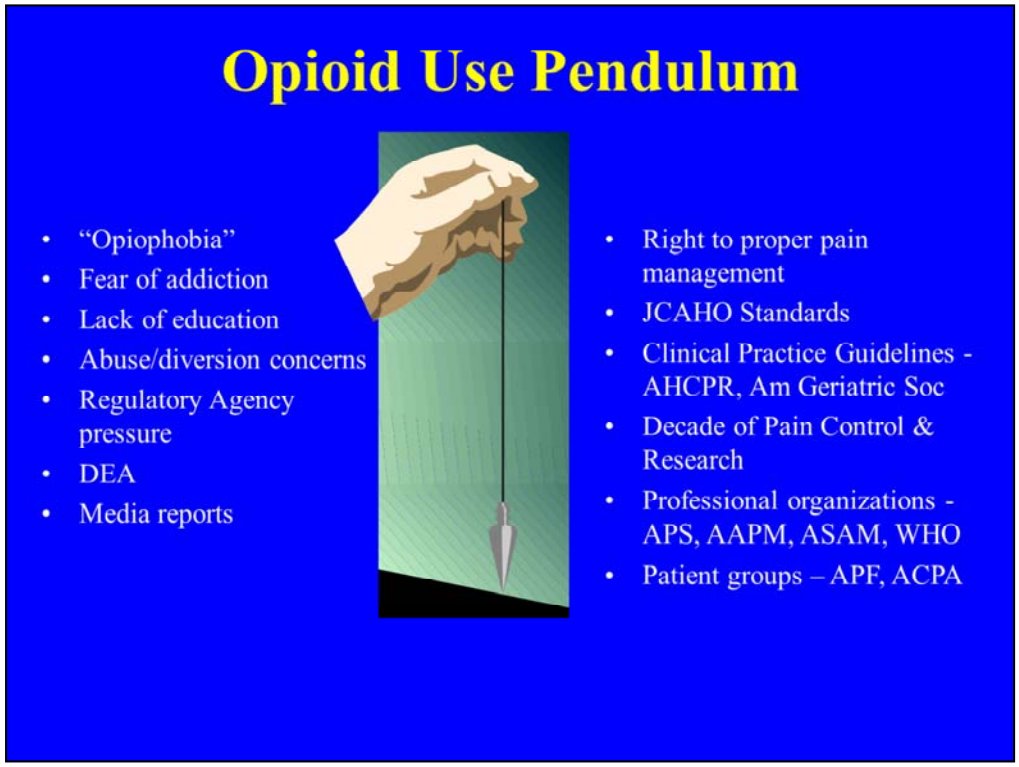
Note: This slide reflects the AHCPR recommendations for dosing opioids. In some cases, these recommendations differ from those contained in the products' package inserts. Please consult the Full Prescribing Information for the Manufacturer's recommended dosing.

1. Acute Pain Management Guideline Panel. Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline. AHCPR Pub. No.92-0032. Rockville, MD; Agency for Health Care Policy & Research. Public Health Service, U.S. Department of Health and Human Services. Feb. 1992.

Barriers to improved pain management faced by clinicians include lack of education, poor pain assessment, and concerns about opioids, especially addiction, respiratory depression, and regulatory scrutiny.[1]

For decades the dangers of opioid analgesics have received far more attention than their benefits. Despite evidence to the contrary, addiction in particular remains an enormous concern of physicians, nurses, patients, and their families and tragically promotes the undertreatment of pain.[1]

1. McCaffery M. Pain management. In: McCaffery M, Pasero C. *Pain: Clinical manual*, 2nd ed. St. Louis: Mosby, 1999:2-10.



The biggest obstacles to rational opioid use are bias and lack of education.[1] Clinicians need to strike a balance between the fears and concerns over abuse & use of opioids, and the patient's right to proper pain management.

Healthcare professionals are still not appropriately trained in clinical pharmacology & appropriate use of these medications, and have an irrational fear of producing addiction, dependence & respiratory depression, as well as fear of increased regulatory scrutiny. [1]

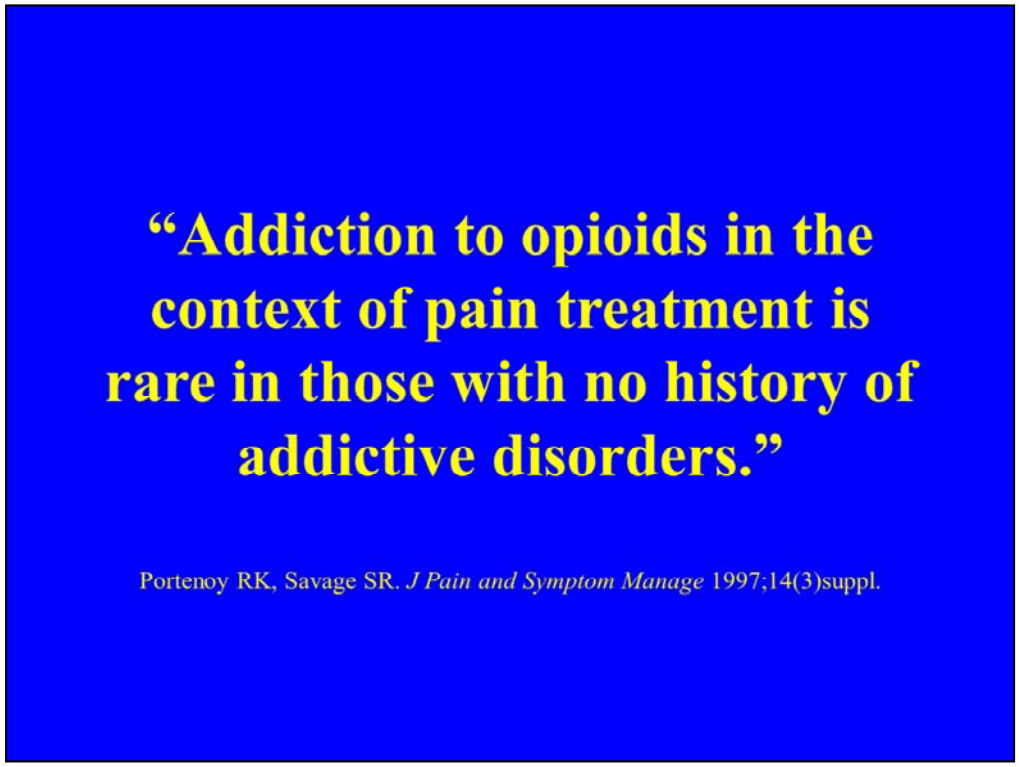
The term "opioiphobia" has been used to describe the syndrome of failure to administer adequate opioid analgesics. Many factors contribute to opiophobia, including: provider pressure, patient pressure, regulatory agency pressure (real or perceived), and lack of education on opioids and pain management principles. [1,3]

Balancing "opiophobia" are the various professional organizations which have recognized the undertreatment of pain and the patient's right to proper pain management. These include the Joint Commission on Accreditation of Healthcare Organizations, which has developed standards for healthcare facilities to ensure assessment and treatment of patients' pain. [3] Organizations such as the AHCPR and American Geriatric society have developed clinical

practice guidelines for treating pain. [4,5] Congress passed a bill providing for the "Decade of Pain Control and Research" to begin on Jan 1,2001 to stimulate further progress in pain research, education and clinical management. [6] Professional organizations such as American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine, and the World Heath Organization have provided leadership and education for physicians related to proper pain management. [2,7] Groups such as the American Pain Foundation and the American Chronic Pain Association provide support and information for people who deal with pain. [8,9]

Reference

1. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, Turk DC (eds.) *Bonica's management of pain*, 3rd ed., pp 1682, 1695, 1705. Philadelphia: Lippincott Williams & Wilkins, 2001.
2. Fear of addiction: confronting a barrier to cancer pain relief. Cancer Pain Release. 1998. Vol 11, No. 3, WHO Collaborating Center on Policy and Communication in Cancer Care, Madison, WI.
3. McCaffery M, Pasero C. *Pain: Clinical manual*, 2nd ed., p 2-10, 730-3, St. Louis: Mosby, 1999.
4. Acute Pain Management Guideline Panel. Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline. AHCPR Pub. No.92-0032. Rockville, MD; Agency for Health Care Policy & Research. Public Health Service, U.S. Department of Health and Human Services. Feb. 1992.
5. AGS Panel on Chronic Pain in Older Persons. Clinical Practice Guidelines. The Management of Chronic Pain in Older Persons. J Am Ger Soc 1998; 46: 635-651
6. Press Release. Decade of Pain Control and Research Begins January 1, 2001. American Academy of Pain Medicine. Glenview, IL. Oct 31, 2000
7. American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine. *Definitions related to the use of opioids for the treatment of pain*. Consensus document. February 2001.
8. Balancing news stories about opioids: a statement on the value of opioids for people with severe pain. April 16, 2001. American Pain Foundation. Baltimore, MD
9. The ACPA Chronicle Newsletter. American Chronic Pain Association. Rocklin, CA



The occurrence of addiction as a result of opioid use for pain relief is extremely rare. Several studies have concluded that the risk is far less than 1%. For example, in a prospective study of 11,882 hospitalized medical patients, only 4 patients could be documented as having become addicted as a result of receiving opioid analgesics. Even more convincing are studies of patients receiving heroin as an analgesic. In England two studies with more than 500 patients who received heroin for pain relief found that no patient could be documented as having become addicted.[2,3,4,5]

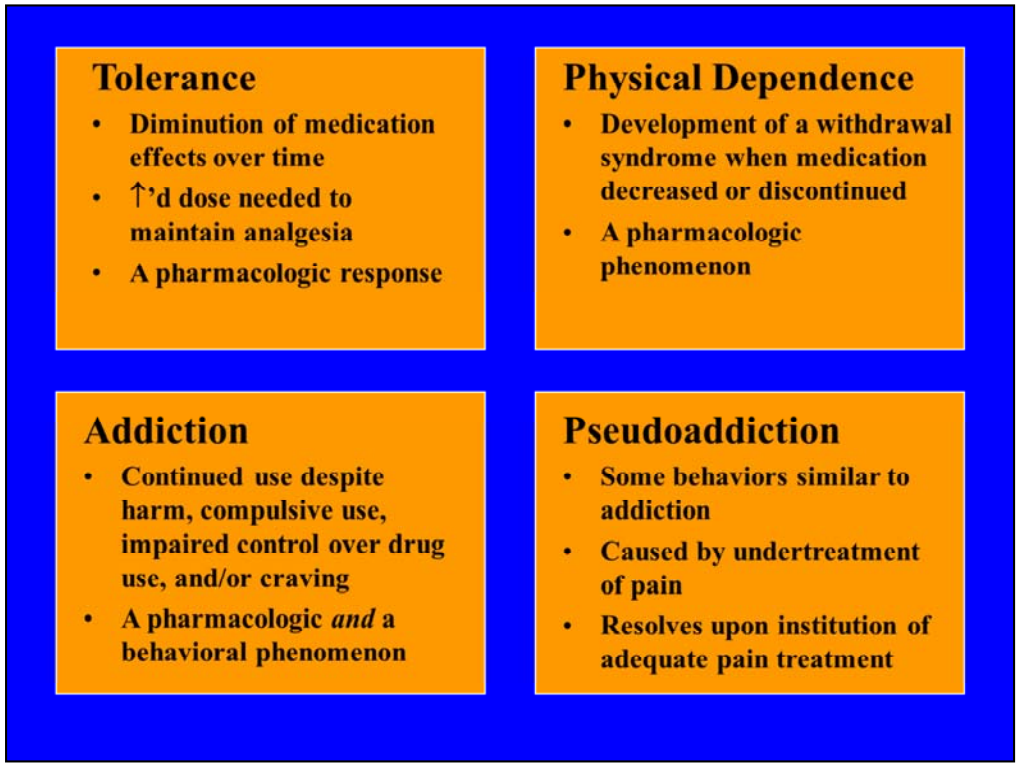
1. Portenoy RK, Savage SR. *J Pain Symptom Manage* 1997;14(3 suppl.):S27-35.

2. McCaffery M. Pain management. In: McCaffery M, Pasero C. *Pain: clinical manual*, 2nd ed. St. Louis: Mosby, 1999:9.

3. Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med* 1980;302:123.

4. Twycross RG. Clinical experience with diamorphine in advanced malignant disease. *Int J Clin Pharmacol* 1974;9:184-198.

5. Twycross RG, Wald SJ. Long term use of diamorphine in advanced cancer. In: Bonica JJ, Albe-Fessard D (eds.) *Adv Pain Res Ther* 1976;1:653-661.



Tolerance and physical dependence are both pharmacologic phenomena; addiction and pseudoaddiction include behavioral changes.[1]

Tolerance means that a greater amount of drug is needed over time to maintain a therapeutic effect. Tolerance may also occur to side effects, and thus may be beneficial. Tolerance alone does not mean addiction.[1]

Physical dependence means the development of a withdrawal syndrome when an opioid drug is discontinued. Dependence occurs in almost all patients on opioids, and does not connote addiction.[1]

Addiction is a psychiatric disorder consisting of continued, compulsive use of the substance despite harm.[1]

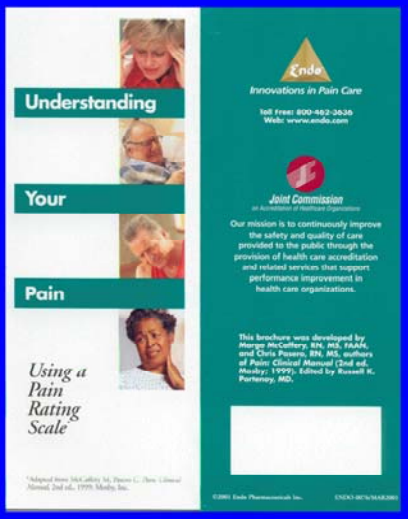
Pseudoaddiction refers to behaviors suggestive of addiction (eg, multiple prescribers, hoarding) when patients are undertreated for pain.[2]

1. American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine. *Definitions related to the use of opioids for the treatment of pain*. Consensus document. February 2001.

2. Weissman DE, Haddox JD. Opioid pseudoaddiction: an iatrogenic syndrome. *Pain* 1989;36:363-366.

JCAHO Pain Standards

- Patients have a right to appropriate pain assessment and management
- Staff, patient & family education on pain management required
- Documentation of pain assessment & management activities required
- Standards apply to hospitals, outpatient clinics, nursing homes, home care agencies, and other accredited facilities



The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has developed new standards for the assessment and management of pain in hospitals and other healthcare settings. A key to these new standards is the emphasis of the patients' right to appropriate assessment and management of pain. These newly developed standards have been endorsed by the American Pain Society. Since January 2001, these standards have been scored for compliance.[1]

The introduction of these standards is the product of a two-year collaborative effort between the Joint Commission and the University of Wisconsin-Madison Medical School. This effort was part of a project funded by the Robert Wood Johnson Foundation to make pain assessment and management a priority in the nation's health care system.[1]

1. Joint Commission on Accreditation of Healthcare Organizations, Oakbrook, IL (www.jcaho.org)